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PENICILLIN AS A CHEMOTHERAPEUTIC AGENT *

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IN 1929, while examining plates seeded with staphylococci, Fleming [1] observed that colonies failed to grow in the neighborhood of a colony of a contaminating mold. Following up this chance observation, Fleming isolated the mold, identified it as a strain of *Penicillium notatum,* and showed that it produced in broth cultures a soluble substance which exerted a remarkable inhibitory effect on pyogenic cocci and the diphtheria group of organisms but not on certain Gram negative rods. He designated the substance as penicillin and suggested that it might be used for differential diagnostic purposes in the cultivation of Gram positive and Gram negative organisms. He further suggested that it might be used as an antiseptic agent.

In 1932 Clutterbuck, Lovell and Raistrick [2] isolated a pigment produced by Fleming's strain of penicillium, but this substance proved to have no antibacterial action. Little further work was done on penicillin until 1940 when Chain and his co-workers [3] at Oxford, stimulated by the work of Dubos [4] on gramicidin, showed that crude preparations of penicillin exerted a remarkable effect in vivo against hemolytic streptococci, staphylococci and pathogenic anaerobes. In 1941 the Oxford workers greatly extended these observations and described a method for small scale production of material suitable for therapeutic use in man.[5] They further showed that penicillin was active in remarkably high dilutions, that it possessed little toxicity and that its action was not inhibited by blood, pus, or tissue derivatives.

The work reviewed in this paper was started in September 1940. Part

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of it has been reported in detail elsewhere.[6, 7, 8, 9] It constitutes a confirmation in part and an extension of the work of the English investigators.

Method of Preparation. Cultures of Fleming's strain of *Penicillium notatum* were grown in a modified Czapek-Dox synthetic medium for eight days at room temperature. After acidification and salt saturation of the culture fluid, penicillin was isolated by extraction with chloroform followed by distribution between aqueous solutions and organic solvents at different pH levels. It has been obtained either as a salt or as the free acid, the latter being more unstable than the salts. The free acid as well as a number of active acyl derivatives has been obtained in apparently crystalline form. Recently stable esters of penicillin have been prepared.[10, 11]

In Vitro Activity of Penicillin. Penicillin has been tested against a wide variety of Gram positive and Gram negative organisms. It is highly effective against Gram positive organisms, both aerobic and anaerobic, and

TABLE I

Susceptibility of Organisms to Penicillin

Susceptible Strains	Insusceptible Strains
Pneumococcus	*H. influenzae*
Streptococcus hemolyticus	*E. coli*
Staphylococcus albus	*B. typhosus*
Staphylococcus aureus	*B. dysenteriae*
Meningococcus	*B. proteus*
Streptococcus viridans	*B. paratyphosus A*
B. subtilis	*B. enteritidis*
Cl. welchii	*B. pyocyaneus*
V. septique	*B. fluorescens*
Cl. histolyticus	*B. prodigiosus*
B. sporogenes	Friedländer's bc.
B. oedematiens	*Staphylococcus albus**
B. sordellii	*Monilia albicans*
Lactobacillus	*Monilia krusei*
Cryptococcus hominis	*Monilia candida*

* Although staphylococci in general are sensitive to penicillin, a number of non-pathogenic *Staphylococcus albus* strains have been isolated which are completely resistant.

against gonococci and meningococci (table 1). Not all strains of the same organism are equally sensitive, but in general strains of pneumococci are more sensitive than strains of hemolytic streptococci, and the latter in turn are more sensitive than strains of staphylococci.

The action of penicillin appears to be either bactericidal or bacteriostatic, depending on the conditions of the experiment. It is active in extraordinarily high dilutions. Experiments with highly purified preparations of penicillin have shown that amounts as little as 0.03 microgram per c.c. are sufficient to inhibit the growth of a 10^{-2} dilution of a culture of hemolytic streptococci containing 200 to 300 million organisms per c.c. It is many thousand times as effective as any of the sulfonamides, its activity being comparable to that of gramicidin and tyrocidin.

The activity of penicillin was compared with that of gramicidin and tyrocidin in the following manner. Cultures of pneumococci, hemolytic

streptococci, and staphylococci were treated with similar concentrations of gramicidin, tyrocidin and penicillin. The cultures were incubated at 37° C. and the organisms per c.c. determined at intervals. The results show that the activity of penicillin is quite comparable to that of the other two substances tested (table 2).

TABLE II

Comparison of Penicillin, Gramicidin, and Tyrocidin in Vitro

Culture	Inhibiting Agent*	Number of Viable Organisms Per c.c.				
		0 Hr.	1 Hr.	3 Hr.	7 Hr.	24 Hr.
Pneumococcus (D/39)	Penicillin†	2,200,000	585,000	7,200	200	0
	Gramicidin	2,200,000	1,860,000	33,500	0	0
	Tyrocidin	2,200,000	0	0	0	0
Streptococcus hemolyticus (C203Mv)	Penicillin†	1,500,000	4,300,000	2,650,000	420,000	0
	Gramicidin	1,500,000	2,430,000	1,140,000	7,000	2,400
	Tyrocidin	1,500,000	100	0	0	0
Staphylococcus aureus (Oxford)	Penicillin†	7,750,000	13,900,000	700,000	73,500	0
	Gramicidin	7,750,000	490,000	2,400	0	0
	Tyrocidin	7,750,000	24,000	2,900	1,850	1,750,000

* 10 micrograms per c.c. of each used.

† Activity of penicillin preparation used in these experiments was approximately 100 Oxford units per mg.

Similar experiments were carried out with sulfathiazole and sulfanilamide. It was found that penicillin causes an actual diminution in the number of organisms, whereas sulfanilamide and sulfathiazole cause only a decrease in the rate of multiplication of the organisms (table 3).

TABLE III

Comparative Effect of Penicillin and Sulfonamides on Growth of Hemolytic Streptococci in Vitro

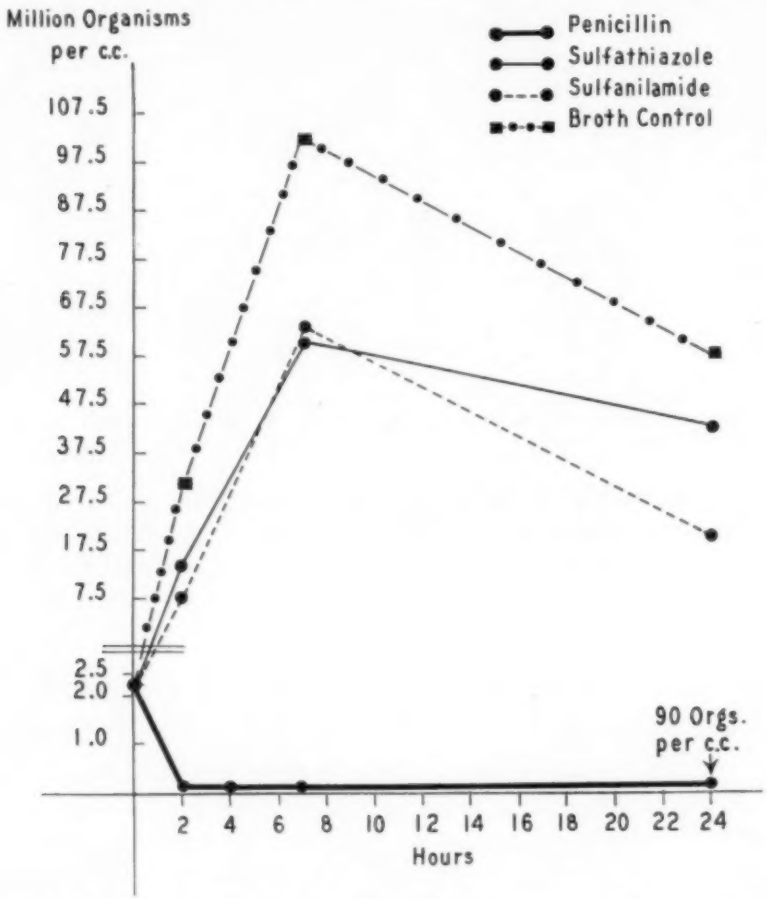
Drug 1 : 10,000 Dilution	No. Hours Incubation			
	0	4	7	24
Penicillin*	2,500,000	218,000	90,000	90
Sulfanilamide	2,500,000	10,100,000	65,000,000	20,900,000
Sulfathiazole	2,500,000	14,000,000	61,000,000	40,000,000
Broth Control	2,500,000	29,300,000	101,000,000	55,400,000

* A crude preparation containing approximately 500 Oxford units per c.c. was used in these experiments.

This is also illustrated by graph 1 in which the number of organisms per c.c. is plotted against time. Further experiments indicated that the action of penicillin is not inhibited by blood or serum (graph 2).

In Vivo Activity. In vivo penicillin has an equally remarkable effect. Mice were infected intraperitoneally with a highly virulent strain of *Strep-*

tococcus hemolyticus and treated with small amounts of penicillin subcutaneously. The results of an early experiment with a crude preparation are shown in table 4. Animals were infected with amounts up to 2 c.c. of whole culture, containing at least 10 million lethal doses. The total amount of penicillin given to each animal was calculated to be approximately 7 mg. of the crude preparation, representing less than 350 Oxford units.[5] Sixty-six per cent of animals receiving 2 c.c. and 90 per cent of animals receiving 1 c.c



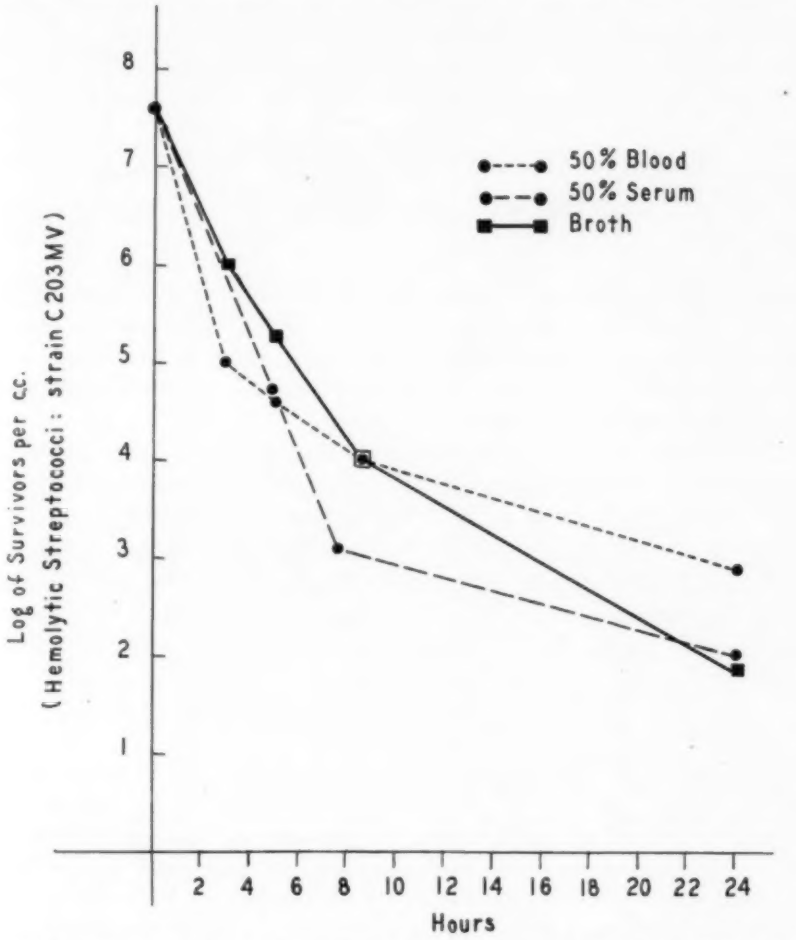
GRAPH 1. Comparative effect of penicillin and sulfonamides on growth of hemolytic streptococci in vitro.

of whole culture survived or showed prolonged life. Untreated controls receiving 1 c.c. of a 10^{-7} dilution all died within 48 hours.

In a subsequent experiment a titration of the activity of a more potent preparation of penicillin was carried out. It was found that 0.75 mg. of a preparation containing 150–200 Oxford units per mg. protected against 1 c.c. of a 10^{-2} dilution of a highly virulent strain of hemolytic streptococci (C203Mv)—(table 5).

In further experiments it was shown that penicillin is effective against hemolytic streptococcal infections when the penicillin is given intraperitoneally as well as when given subcutaneously.

In the experiments so far described treatment was instituted simultaneously with or shortly following infection. In other experiments it was



GRAPH 2. Effect of blood and serum on bacteriostatic action of penicillin in vitro.

found that mice could be successfully treated when the drug was administered as late as eight hours after infection.

Similar experiments were carried out on two strains of meningococcus Type I. The organisms * were grown on blood agar for six hours and then washed off into a small volume of physiological saline. This suspension was diluted with saline to a turbidity equivalent to a No. 1 MacFarland

* Meningococcus cultures were obtained from Dr. Hattie Alexander of the Babies Hospital, New York City.

TABLE IV

Effect of Subcutaneous Injection of Penicillin on Group A Hemolytic Streptococcus Infections (C203Mv)

Dilution of Culture	Number of Organisms Injected (×1,000)	Number of Mice	Amount of Penicillin* (c.c.)	Number of Days Treated	Number Dead (<48 hr.)	Number Prolonged Life (2–7 days)	Number Survived (>7 days)
2.0 c.c.	180,000	9	0.4–0.65	<6	3	1	5
1.0 c.c.	90,000	10	0.4–0.6	<6	1	2	7
10^{-1}	9,000	15	0.2–0.58	<6	2	4	9
10^{-2}	900	13	0.2–0.57	<6	0	4	9
10^{-3}	90	11	0.2–0.57	<6	0	3	8
Controls							
10^{-7}	0.009	15	0	0	15	0	0

* A crude preparation containing approximately 500 Oxford units per c.c. was used in these experiments.

Standard. Serial dilutions were made in 7 per cent mucin according to the method of Alexander [12] and 1 c.c. of a 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6} dilution injected intraperitoneally into a small series of white mice. Penicillin mixed with three volumes of sesame oil was given by the subcutaneous route ½ hour, 18 hours, and 24 hours after injection.

Although the number of animals is small, it is apparent that 1800 Oxford units of penicillin afforded almost complete protection against 10^{-5} and 10^{-6} dilutions of meningococci and partial protection against 10^{-3} and 10^{-4} dilutions. Untreated controls died in less than 24 hours (table 6).

Likewise, experiments were carried out on *Cl. welchii* and *Cl. septique* infections in guinea pigs. Cultures of *Cl. welchii* and *Cl. septique* * were grown in plain broth for 48 hours under anaerobic conditions and then

TABLE V

Titration of Activity of Penicillin * against Hemolytic Streptococci in Vivo

Dilution of Cultures	Penicillin (mg.)	Number Mice	Number Survived
10^{-2}	1.5	3	3
	1.0	3	3
	0.75	3	3
10^{-1}	1.5	3	3
	1.0	3	3
	0.75	3	0†
Undiluted	1.5	4	4
	1.0	4	2†
Controls			
10^{-6}	0	10	Died <2 days
10^{-7}	0	10	Died <2 days

* Ammonium salt containing 150–200 Oxford units per mg.
† Two mice showed prolonged survival time in each instance.

* *Cl. welchii* (Strain 45) and *Cl. septique* (Strain 37) were used throughout. Cultures were obtained through the kindness of Dr. Frederick Humphreys of the College of Physicians and Surgeons, Columbia University, New York.

centrifuged. The cells were taken up in one volume of sterile distilled water and the suspensions heated at 80° C. for one hour. The resultant toxin-free suspensions were used in all animal inoculations.

Guinea pigs, weighing 300 to 350 grams each, were used for all experiments with *Cl. welchii*. White mice, weighing 18 to 20 grams, were found satisfactory for infection with *Cl. septique*. Equal volumes of spore suspension and of 10 per cent calcium chloride were injected simultaneously. All injections were given by the intramuscular route. Penicillin † treatment was started one hour after infection and was administered subcutaneously

TABLE VI

Effect of Penicillin on Experimental Infections Due to *N. meningitides*, Type I

Culture		Amount of Penicillin (Oxford Units)	Number of Mice	Number Died	Number Survived	Per Cent Survived
Strain	Amount					
Ombelet	10^{-3}	1,800 0	2 2	1 2	1 0	50 0
	10^{-4}	1,800 0	4 3	2 3	2 0	50 0
	10^{-5}	1,800 0	5 3	1 3	4 0	80 0
	10^{-6}	1,800 0	5 3	0 3	5 0	100 0
McNally	10^{-3}	1,800 0	4 3	1 2	3 1	75 33
	10^{-4}	1,800 0	5 3	2 2	3 1	60 33
	10^{-5}	1,800 0	4 2	0 2	4 0	100 0
	10^{-6}	1,800 0	5 3	1 3	4 0	80 0

once every 24 hours over a three day period. The penicillin used was dissolved in a small volume of saline and the solution mixed with three volumes of sesame oil. The dosage throughout was comparable to that which gives complete protection in mice against large infecting doses of virulent hemolytic streptococci.

Seventy-five per cent of the mice infected with 0.005 c.c. of a suspension of *Cl. septique* spores (approximately 1–2 MLD's) were protected by 434 Oxford units of penicillin. Approximately 50 per cent were protected against 0.01 c.c.–0.02 c.c. of such a spore suspension. No protection was obtained against 0.04 c.c.

All of the guinea pigs infected with 0.1 c.c. of a suspension of *Cl. welchii*

† We are indebted to Charles Pfizer and Company, Brooklyn, New York, for the penicillin used in these experiments.

spores (1–2 MLD's) were protected by the injection of 666 units of penicillin. There was no protection against 0.2 c.c. of spore suspension.

It is apparent that, whereas small amounts of penicillin protect against large numbers of highly virulent hemolytic streptococci, comparable amounts will give partial or complete protection against only two to three lethal doses of *Cl. welchii* and *Cl. septique*. The effect of larger amounts of penicillin on more severe infections by members of the gas gangrene group remains to be determined.

Toxicity. The toxicity of penicillin has been tested in mice, guinea pigs, rabbits, dogs and man. In addition, experiments have been carried out on tissue cultures and in the developing chick embryo. No toxicity was observed with amounts far beyond the range of therapeutic dosage.

For mice the LD_{50}, or the amount necessary to kill 50 per cent of the animals, was 12 mg. of the ammonium salt * † and 32 mg. of the sodium salt.† These amounts are equivalent to 0.666 and 1.8 grams respectively per kg. of mouse weight. Guinea pigs tolerated without visible effect as much as 320 mg. of the sodium salt—equivalent to 1.3 grams per kg. of guinea pig weight. These amounts are far beyond the range necessary for therapeutic dosage.

No toxic effects have been observed from penicillin in tissue cultures on the chorioallantoic membrane, or when applied directly to the human eye.[13] No untoward effects have been observed in man with doses up to 240 mg. or 60,000 Oxford Units of a highly purified product.

Absorption and Excretion. It has been shown that penicillin is absorbed after subcutaneous injection in mice, but that frequent administration is essential to maintain an effective blood level. Small amounts injected every two hours are more effective than large amounts injected at less frequent intervals. Studies on the bacteriostatic and bactericidal properties of the blood of treated animals indicate that penicillin remains in the blood stream for only two to three hours after subcutaneous injection.

Relatively pure preparations of penicillin, some in the form of the free acid and others in the form of the ammonium salt, were tested in rabbits. After intravenous injection of an amount calculated to be sufficient to give a blood level equivalent to three or four times the effective in vitro titer of the same preparation, activity was detected in the circulating blood for three to four hours but not longer.

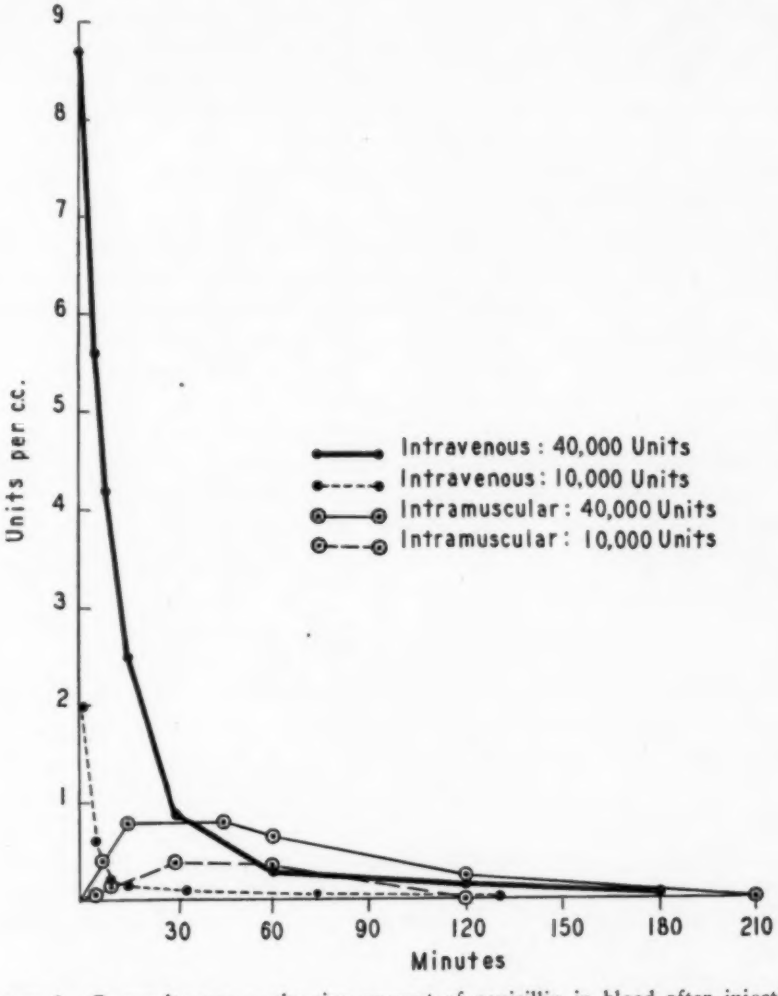
Recently similar experiments have been carried out in man. Single injections of varying amounts of penicillin ‡ were given by the intravenous or intramuscular route. The bacteriostatic action of the blood was determined before and at various intervals after the injection of penicillin.

* The Oxford workers have stated that precipitation with dry NH_3 gas leads to inactivation of the penicillin. We have recovered penicillin quantitatively as the NH_4 salt as a routine procedure when moisture is rigidly excluded from the reaction mixture.

† These preparations contained approximately 200 Oxford units per mg.

‡ We are indebted to Merck & Company, Rahway, New Jersey, for the penicillin used in this experiment.

When penicillin is given by the intravenous route, there is a rapid loss from the blood stream during the first half hour after injection. The rate of disappearance from the blood stream then decreases, and the amount present falls off slowly over a period of two to four hours (graph 3). After this period no detectable amount remains in the circulating blood. These



GRAPH 3. Composite curves showing amount of penicillin in blood after injection.

findings are in general accord with those reported by Rammelkamp and Keefer.[14, 15]

When penicillin is administered intramuscularly, the concentration in the blood stream reaches a maximum within 10 to 30 minutes. This level is maintained from one to two hours, after which time the amount present gradually decreases. After two to four hours penicillin can no longer be

detected in the circulating blood. Although the concentration in the blood is never as high after intramuscular injection, a higher level is maintained for a longer period of time.

The rapidity of excretion is a serious obstacle in the therapeutic use of penicillin. In animal experiments this difficulty has been overcome in part by the use of suspensions in oil and by the subcutaneous implantation of solid pellets. In such forms penicillin is absorbed and excreted less rapidly, and less frequent administration is necessary.[9] In the treatment of human infections, however, these procedures have not proved satisfactory. Efforts have therefore been directed toward the preparation of compounds which will slowly release active penicillin into the circulation. One of the authors (K. M.) has now succeeded in preparing such compounds. Their nature and use are described elsewhere.[10, 11]

Clinical Applications. Clinical use of penicillin has been greatly hampered by two facts: (1) the small yield, and (2) the desire to provide as much material as possible for chemical work. However, a number of cases have been treated with dramatic results. Penicillin has been proved to be effective in man when given intramuscularly, intravenously and intrathecally. It has also proved effective when administered directly into joints and serous cavities as well as in local applications. It is of value in the treatment of infections due to hemolytic streptococci, pneumococci, gonococci, meningococci and staphylococci. In particular, it has proved effective in cases resistant to sulfonamide therapy. The number of cases so far treated is small, but the results are highly encouraging. Up to the present time no serious toxic effects have been observed.

Summary

Penicillin is a chemotherapeutic agent exhibiting a remarkable antibacterial action against Gram positive organisms and against gonococci and meningococci. It is not effective against Gram negative bacteria. Its activity is of a totally different order of magnitude from that of any of the sulfonamide compounds.

Penicillin is effective both in vitro and in vivo. It is active in the presence of pus and inflammatory exudates. Its action appears to be either bactericidal or bacteriostatic, depending upon the conditions of the experiment.

Penicillin appears to be completely non-toxic in doses far exceeding those necessary for therapeutic purposes.

Penicillin is rapidly excreted through the kidneys and frequent administration is necessary to maintain an adequate blood concentration.

Penicillin promises to be a chemotherapeutic agent of great clinical value.

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REACTIONS TO PARENTERAL FLUID ADMINISTRATION *

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This review will discuss briefly the reactions to intravenously administered fluids in general, such as whole blood, plasma, human serum and crystalloid solutions. It will deal particularly with the question of reactions to plasma, since this material is now widely used and lately its rôle as an actual or potential source of reactions has been a controversial point.

The causes of reactions may be inherent in the fluid administered or may be conditions (physiological or pathological) peculiar to the recipient or to a combination of these two factors.

Some of the elements causing reactions, such as pyrogens, may be found in all of the fluids mentioned, whereas others are present or greatly prevailing only in certain fluids. Thus, hemolytic reactions have been reported practically only when erythrocytes have been administered. Often reactions are traced not to the fluid itself, but to improperly cleaned equipment used to prepare or administer the fluid. This is particularly true of pyrogenic reactions.

The most common reactions due to causative elements inherent in the fluid alone may be classified as pyrogenic, nitritoid, embolic or mechanical (from speed of administration). Reactions due to inherent qualities of the fluid combined with conditions of the patient may be listed as hemolytic and allergic. Conditions inherent in the recipient alone which increase the incidence of reactions may be listed as hyperhemolysis, liver disease, hypoproteinemia and cardiac insufficiency. Free hemoglobin, potassium content, temperature and air embolism are elements often mentioned as potential or actual causes of reactions which will also be briefly mentioned.

The hemolytic reactions following whole blood transfusion will be commented upon briefly in view of the fact that the subject has been covered by previous publications.

Pyrogenic Reactions

Pyrogenic reactions are by far the most common and may occur after the intravenous administration of any fluid which has been improperly prepared or administered with improperly prepared apparatus. Pyrogens, strictly speaking, are any substances which will provoke a febrile reaction after intravenous administration. Pyrogens are usually the product of bac-

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terial growth and disintegration of bacterial bodies—certain bacteria, particularly gram negative varieties, produce more pyrogens than others.

The presence of pyrogens in poorly prepared or poorly preserved distilled water [1] and the ease with which glassware and apparatus become contaminated explain the relative frequency of pyrogenic reactions. In addition, blood, plasma and serum are relatively good media for bacterial growth, and a minimal chance contamination may be followed by bacterial growth sufficient to cause extremely severe reactions, when the material is used intravenously.

The pyrogen content of water varies considerably with the source from which it is obtained. It also varies with conditions favoring bacterial growth. Thus, still or slow-moving surface water, particularly in summer, may be expected to have a high pyrogen content whereas water from deep or artesian wells or spring water, protected from surface contamination, may be expected to be relatively pure. Practically all tap water contains pyrogens. These pyrogens cannot be removed or rendered harmless by sterilization by heat and they will pass through sterilizing filters. Co Tui and McCloskey, however, claim that it is possible to remove pyrogens by filtering through Seitz, No. 3 serum pads twice.[2] The only effective practical means of removal of pyrogens is by proper distillation. Proper distillation requires transforming the water to a pure dry gas followed by condensation to the liquid state.

Fresh properly distilled water is pyrogen-free and is often referred to as "parenteral." If distilled water contains pyrogens, it is usually due to one of three causes. First, the still or the container used to collect the distillate is contaminated. Second, the still is not properly constructed, so that droplets of water are entrained with the current of steam and carry pyrogens with them. Third, the water may be perfectly distilled but allowed to stand for several hours before sterilization so that bacterial contamination occurs. In addition, if the original water is heavily contaminated, the distillate is more likely to contain pyrogens. It is desirable, therefore, to start with as good a water as possible, and in all events to operate the still at a rate about half of the rated capacity. The water still must be equipped with a suitable trap or baffles to eliminate droplets of undistilled water. The still and storage chamber may be sterilized by running live steam through them each morning. Following this, the first 30 minutes, distillate should be merely considered a wash for the apparatus and discarded. No distilled water should be used after three to four hours unless it has been sterilized in a sealed container.

Pyrogenic reactions vary from very mild to extremely severe. The pattern is fairly constant. The reactions start within a very short time after the administration or during the administration, and consist of chill or temperature rise or both with a sense of malaise and occasionally nausea. The reaction is usually over in a few hours, very seldom lasts over eight hours. In extremely severe cases, high temperature is followed by circulatory col-

lapse. There is no satisfactory treatment of pyrogenic reactions, except symptomatic. Therefore, the remedy is prevention.

Human blood, plasma and serum do not originally contain pyrogens. They may, as stated, become contaminated if not properly prepared and preserved. These fluids do not lend themselves well to sterilization, although serum and, with proper procedure, plasma may be passed through sterilizing filters. This will not, however, remove pyrogens even if bacteria responsible for their production are removed. Filtration of blood or plasma with improperly prepared gauze filters or similar devices to remove fibrin flocculi is a not uncommon source of pyrogens.

The maintenance of such fluid as blood plasma and serum at refrigerator temperature (plus 2 to plus 8° C.) for relatively long periods of time slows, but does not eliminate the growth of certain bacteria. Likewise, the addition of mercurial antiseptics as bacteriostatic agents does not solve the problem. If these antiseptics are added in such concentration as to be fairly effective, the total amount of mercury may be too large when massive doses of plasma or serum are employed. If, on the other hand, the concentration of the antiseptic is low enough to avoid toxicity (merthiolate 1: 35,000, phenyl-mercuric-borate 1: 50,000), the presence of proteins in high concentration makes the action of the preservatives extremely doubtful. The addition of sulfanilamide [3] has not been found to be effective as was at first thought.[4]

Even careful bacterial studies are not an absolute assurance against severe pyrogenic reactions from this source in plasma or serum preserved in the liquid state. Only a small portion of such material, at best 2 per cent of the total volume,[5] is used in tests for sterility. Under such conditions, contamination with few bacteria may easily be missed, but subsequent growth of bacteria may cause very severe reactions.[6]

To guard against the formation of pyrogens in blood, plasma and serum it is necessary to take every precaution to prevent bacterial contamination. These precautions include asepsis in the collection of blood, and the preparation of plasma and serum by a closed method. A closed method is one which does not allow exposure to unsterile air at any time during the process.[7] In addition, plasma and serum should always be cultured and not released for use until proved sterile. It is not practical to culture whole blood since it would be several days old before results of cultural studies would be available. Citrated blood must be stored in a refrigerator at +2 to +4° C., immediately after collection and until used, to minimize bacterial growth if a chance contamination should occur. The period of storage should be as short as practicable. Plasma or serum for routine use should be stored in the frozen state. Storage in the frozen state will prevent bacterial growth. In the past, many transfusions of fresh blood have been given by an open method without excessive reactions. The reason is simply that the few bacteria which were contained in the blood were not given sufficient time to grow and cause reaction but if the blood had been stored, the organisms

would have multiplied and might have caused severe reactions. Preservation of plasma or serum in the dried state is also a safe method. Guarding against bacterial contamination of blood, plasma or serum does not of itself assure absence of pyrogens: glassware and rubber tubes must be pyrogen-free to avoid contamination.

It is possible, but not always practical, to test the pyrogenicity of plasma, serum and crystalloid solutions by animal injection. The results found in the animals, usually rabbits, are on the whole comparable to those found in man if a careful technic is followed.[8] The test is usually more apt to show a false positive than a false negative result. Distilled water may be chemically tested for presence of reducing substance.[9] A positive test indicates poor water but a negative test does not insure the absence of pyrogens. Distilled water may also be tested for its electrical conductivity. Here again a positive test (high conductivity) means poor water but a negative test (low conductivity) does not mean that pyrogens are absent.

The reactivity of both experimental animals and man to pyrogenic substances contained in fluids administered intravenously varies greatly. This is of importance both in testing solutions by inoculations in experimental animals such as rabbits and in evaluating pyrogenic reactions in man. When using rabbits for pyrogenic tests, the animals should be selected so as to eliminate both the hyper-reactive and the hypo-reactive.

Some patients will show no reaction to a given solution which may be mildly or moderately pyrogenic to other individuals. The amount and speed of administration also play a part. A small amount of mildly pyrogenic solution given slowly is not nearly so likely to cause a reaction as is a large amount given rapidly. Another obvious factor to be taken into account is the recipient's blood volume, which determines the final concentration of pyrogenic substances, all other conditions remaining constant.

Aside from the pyrogens contained in the fluid itself, there is another and perhaps even more common cause of pyrogenic reactions. This is the glassware and rubber tubing used to prepare and administer the material. Dirt and dust which may be allowed to collect in glassware may cause chill-fever reactions. Excess of sulphur which is found on most new compound rubber tubing may also cause reactions if it is not properly removed. All too often used bottles and tubing are allowed to stand wet for many hours under conditions favoring bacterial growth and then not adequately cleaned. Under such conditions pyrogenic reactions are the rule rather than the exception. The remedy is: (1) avoid contamination of the fluids remaining unused after administration; (2) proper cleaning of glassware and other apparatus, followed by rapid drying or sterilization; (3) distilled water should not be stored for over three hours after preparation unless sterilized.

With well prepared crystalloid solutions, the incidence of pyrogenic reactions is extremely small, less than one per thousand even with very large doses. With whole blood, the reactions of this type are more common, varying from 2 to 5 per cent. In well preserved plasma or serum they are

well below 1 per cent. Recovery is generally rapid and complete even in relatively severe reactions, save those followed by circulatory collapse.

In patients with a febrile temperature, especially if of the septic type, the intravenous administration of fluids, especially whole blood often causes a greater temperature rise. It is desirable in these cases, whenever possible, to administer the intravenous fluids at a time when the temperature is at its expected low, usually in the morning.

Nitritoid Reactions

These have been observed after administration of whole blood but are more common after the administration of freshly prepared serum or fresh serum which has been kept in the frozen state or dried from the frozen state. It has not been observed after the administration of crystalloid solutions. Usually the reaction immediately follows the administration of the fluid; in fact, it often occurs during the administration.

The reaction consists of a sense of constriction of the chest, often very alarming, pain over the lumbar region, sometimes, but not always, followed by chill and/or rise of temperature and occasionally by nausea, vomiting and headache. The reaction is usually over after a few hours (four to five hours) and appears to cause no permanent damage.

We have recently observed, through the courtesy of Dr. Angelucci and Dr. Minot, a patient who had severe reactions of the type here described following the administration of fresh whole citrated blood, and of dried pooled commercial plasma.

The patient, a 20 year old white girl, was suffering from severe anemia as a result of uterine bleeding. At 5 p.m. on June 8, 1943, she was given a transfusion of well matched group O blood, the patient also being group O and Rh positive. After 100 c.c. had been administered, the patient complained of an unusual feeling in the throat, tightness of the chest, and shortness of breath. The transfusion was stopped and was started again after symptoms had subsided. Cough and dyspnea became severe and the transfusion was discontinued. The patient was pale, nauseated and vomited. The pulse was weak, thready; the blood pressure was 130 mm. Hg systolic and 50 mm. diastolic. One hour after transfusion, the patient had a chill and the temperature rose to 104° F. The patient recovered promptly and the temperature returned to normal overnight. The blood had been collected in a commercial vacuum type bottle and was given immediately upon collection. At 11:30 a.m. on June 10, the patient received another transfusion of fresh whole citrated blood. After 10 to 20 c.c. of blood had been administered, the patient had a reaction similar to that reported above. A skin test with citrated whole blood and with plain sodium citrate was negative.

On June 18, the patient received a transfusion of citrated "lyophilized" plasma (Sharpe and Dohme) regenerated from the dried state. After only 10 c.c. had been administered, the patient complained of severe abdominal pains, accompanied by nausea and vomiting. Within one hour of the administration, there appeared a purpuric rash over the shoulders, arms and neck. The temperature rose to 103.6° F. The patient returned to her normal condition overnight. On July 9, the patient received a specimen of citrated blood obtained by gravity and with all possible precautions to avoid pyrogens. The blood transfusion was started at 11:30 a.m. at the rate of about 2 c.c. per minute. At 11:43 (when approximately 26 c.c. of blood had

been administered), the patient complained of abdominal discomfort, tightness of the chest accompanied by dyspnea and vomiting. The pulse became very rapid and weak; the systolic blood pressure increased from 110 to 138 mm. Hg and then gradually returned to 112 mm. Hg in a period of two hours, and the diastolic fell from 80 to 0 during the same period of time. This reaction was accompanied by chill and fever. Transitory cyanosis occurred about 30 minutes after the administration.

The patient was given saline and glucose solution repeatedly. Six hundred c.c. of saline containing 4 grams of sodium citrate were administered intravenously without reaction. On July 15 and July 17 the patient was also given washed red blood cells suspended in saline solution without reaction. On both occasions the red cells were those obtained from 500 c.c. of whole blood. The cause of reactions appears to be in the plasma itself.

These reactions have been observed after the use of very fresh serum but not after the use of serum which has aged for some time either at room temperature or at refrigerator temperature. Self and Scudder's recent work [10] tends to confirm these findings. It is therefore presumed that at least some of these reactions may be due to a substance or substances which are present in fresh serum and not in aged serum, or if present, in lesser amounts. It is further argued that since the intravenous administration of fresh plasma very seldom gives rise to nitritoid reactions, it is likely that the substance or substances responsible for at least some of the nitritoid reactions are a product of blood clotting. This was observed by Brodie as far back as 1900.[11]

For these reasons it is possible that one of the substances causing nitritoid reactions might be thrombin, which is formed in excess during the process of clotting. Investigative work is now in progress to determine the parallelism, if any, between the decrease of skin reactivity to intradermal injection of serum [12] and the decrease of thrombin content in a specimen of serum allowed to stand at room temperature.

Nitritoid reactions may not be entirely eliminated, but with the use of properly prepared whole blood or plasma they are sufficiently rare and relatively mild so that they need not constitute a major preoccupation.

Embolic Reactions

Embolic reactions are not encountered in the administration of crystalloid solutions. These should not be filtered through paper or gauze, but through a sintered or fritted (glass) filter before sterilization. They need not be filtered again before administration. Whole blood should always be filtered immediately before administration. This is particularly important for blood preserved at refrigerator temperature for a period of time because of the rapid and progressive formation of numerous fine, soft flocculi.

Plasma and serum should always be filtered at the time of preparation, preferably at the time of pooling. If properly preserved thereafter, as mentioned below, they need not, strictly speaking, be filtered before administration. This is the practice which we have followed for a number of years [6, 13]

with plasma frozen immediately after pooling and filtration and maintained in the frozen state at — 20° C. or lower, and thawed before use in a circulating water bath at plus 37° C. To maintain this material free from flocculation, it must not be stored in the refrigerator after thawing, but kept at room temperature until used, as pointed out later. However, unless all steps of preservation and regeneration of plasma are under careful and dependable control, it is necessary to filter these fluids immediately before administration.

Embolic reactions so far have been rare. With plasma we know of only one case which seems fairly well established. This was brought to our attention by Dr. Cooksey of Detroit and by Dr. J. H. Lewis, who attended the patient.[6, 14] The patient, a boy, received 90–100 c.c. of undiluted, unfiltered plasma during a period of 20–25 minutes. Asphyxial death was sudden and occurred while the plasma was still being administered. This plasma had been separated from citrated blood by sedimentation for about 24 hours after collection of the blood. It had been preserved in the liquid state for 40–50 hours at refrigerator temperature. Microscopic examination of the lungs showed the smaller branches of the pulmonary artery to be plugged by a pinkish staining material, with a coarse reticular structure, closely resembling fibrin. Sections from other organs showed no such changes, presumably because the fibrin-like precipitates had not gone through the filter of the lungs.

The severity of this type of reaction and the ease with which it can be avoided should call everyone's attention to the elimination of any flocculi or fibrin precipitate. The most common cause of flocculation is the preservation of whole blood or plasma at refrigerator temperatures (2° to 8° C.). As far as whole blood is concerned, refrigeration is a necessity, and the only way to eliminate the danger of embolic reaction is carefully to filter the blood immediately before administration. However, flocculation of plasma may be entirely avoided by preserving plasma either in the frozen or dry state.

If plasma is to be kept in the liquid state for any period of time, it should be at room temperature, when flocculation does not occur for a period of four to six weeks and then very slowly. Flocculation may also be appreciably retarded in plasma by the addition of glucose solution.[15] Excessive dilution, however, must be avoided.

Effective filtration of flocculi, particularly thread-like precipitates of fibrinogen, is easily accomplished by the use of four layers of 40-mesh gauze, or equivalent material. The use of the standard 200 mesh stainless steel gauze is equally satisfactory, but quite expensive for generalized use. Good results have also been obtained by Dr. S. Brandt Rose[16] by the employment of a single layer of nylon cloth with 150–160 mesh per square inch.

Speed of Administration

Concerning the speed of intravenous administration of fluids, it is safe to state from practical experience and from the experimental work of

Altschule et al.[17] that if the concentration is isotonic, a rate up to 20 c.c. per minute is perfectly safe and well tolerated. However, this rate may be altered, either up or down, depending upon the need of more rapid blood volume replacement or the patient's cardiac condition. Thus, in patients in very severe shock, it is necessary to administer intravenous fluids, particularly plasma or blood at a much faster rate than that just mentioned. As much as 500 c.c. of material can be administered in a period of 10 minutes. Beyond this quantity, it is advisable to reduce the rate of administration.

On the other hand, in a patient in whom cardiac weakness is suspected, rates of fluid administration not exceeding 10 c.c. per minute should be advised. This is particularly true for the administration of whole blood because of its higher viscosity. Under these conditions, a rate of 5 c.c. per minute appears desirable. Within these limits it is reasonable to assume that the danger of reaction from speed of administration can be ignored.

However, excessive speed of transfusions must not be considered a source of reaction only through increased venous pressure. Speed is a very important factor in determining the rate and severity of transfusion reaction due to chemical factors contained in the transfusion fluid. Thus if pyrogens are present in a low concentration and the rate of transfusion is slow, no reaction may result. With increased speed, however, the concentration of pyrogens may at any given moment rise sufficiently to cause severe reactions. It is also to be noted that if the speed is slow, transfusion may be stopped, if necessary, before the reaction becomes too severe.

In at least two cases of transfusion of incompatible blood, in our own experience, fatal reactions were avoided probably because the rate of transfusion was slow and symptoms developed when only a relatively small amount of blood had been administered. This allowed the transfusion to be stopped in time to avoid more serious damage.

When not dealing with an emergency, therefore, administer the fluids at the slowest rate compatible with good results, generally not over 20 c.c. per minute. Patients should, as much as possible, be under observation when receiving intravenous fluids, particularly whole blood, plasma or serum.

Hemolytic Reactions

Hemolytic reactions are comparatively rare but, because they are often fatal, it is important to take every precaution to avoid them. By far the great majority follow transfusion of whole blood into recipients whose plasma agglutinates the donor's cells. The possible rôle of the administration of plasma, serum and universal donor blood in producing hemolytic reactions will be discussed. Isotonic and hypertonic solutions of sodium chloride or dextrose have not been shown to cause such reactions. Theoretically a large intravenous infusion of distilled water should produce hemolysis, but Schemm[18] has reported at least two cases in which 1,000 c.c. of distilled water were unintentionally administered in the space of one hour

without adverse reaction. Similar occurrence should, of course, be carefully avoided.

In this paper a hemolytic reaction refers to the syndrome which follows the transfusion of incompatible blood. Blood is incompatible if the recipient's plasma agglutinates the donor's cells.

The typical hemolytic reaction starts during or very shortly after the transfusion. It commonly manifests itself by a chill, often followed by fever, nausea, vomiting, pain in the lumbar region and a sense of constriction in the chest. There may be abdominal cramps, pain over the bladder and an urge to defecate. Transient hemoglobinemia with passage of scanty reddish-brown urine is followed within five hours by hyperbilirubinemia, and shortly after by jaundice, usually reaching the peak within 24 hours. The oliguria may improve and the patient rapidly recover, but more often azotemia follows. This may lead to uremia and death or, after a period of several days when the issue is in doubt, the flow of urine increases and recovery follows. In a number of cases the patient may die even though the urinary output has become normal or even larger than normal. In these patients the nitrogen content of the urines is very low.

Laboratory examinations should be carried out to ascertain the diagnosis whenever a suspicion exists that a hemolytic reaction has occurred. The examination of the first urine passed after a hemolytic crisis reveals the presence of albumin, hematinic casts, hemoglobin and erythrocytes. A specimen of blood should be obtained immediately after the reactions and about five and 12 hours later. Hemoglobin in the plasma of the first specimen reveals that hemolysis has occurred. An increase in the bilirubin content of the second specimen as compared with the first further confirms the diagnosis. The peak of the bilirubinemia is generally reached between the fifth and the eleventh hours after the crisis.[19] Many theories have been advanced concerning the pathogenesis of the sequelae of the hemolytic reactions.[20] A critical review of these seems beyond the scope of this paper.

To our knowledge, there is no treatment which has proved uniformly successful. Alkalinization, renal decapsulation or sympathectomy, pelvic lavage, blood and plasma transfusion and many other procedures have been advocated. In any event, it seems logical to maintain an adequate fluid intake and an adequate blood volume.

The prognosis in any given case is somewhat difficult to determine. In general, in patients suffering from previous kidney damage or from any other serious illness, the outlook is unfavorable. The amount of blood administered seems to bear some relation to the end result. Most patients receiving 250 c.c. or less will recover from their first hemolytic transfusion reaction. Those receiving 500 c.c. or who have had previous transfusion reactions will usually die.

In view of the lack of any satisfactory treatment, it is absolutely essential to take every precaution to prevent hemolytic reactions. These precautions include a careful blood grouping of the recipient and the donor, care-

ful cross-matching tests, adequate studies regarding the anti-Rh and other less common isoagglutinins particularly in pregnant or puerperal women, and in persons receiving repeated transfusion. In addition, the transfusion should be given slowly so that it may be stopped early in the event of a reaction. Unfortunately, in some patients, the transfusion of incompatible blood is not followed by immediate reaction, and the first signs are passage of dark-colored urines and jaundice, followed by oliguria or anuria. It is our practice to use plasma as much as possible in place of whole blood, especially in emergency cases in which mistakes in blood grouping or matching may be the result of haste. There are very few patients who will not respond to plasma at least until a whole blood transfusion may be carefully planned.[6]

The preparation for a blood transfusion must be done by a well trained person. Adequately trained personnel must always be on call for such work.

The sera used for blood grouping must be of high potency. This means that blood grouping sera must be specific, of high titer and rapidly acting. They must be checked at regular intervals against cells of known groups. These cells are best obtained from thoroughly tested personnel of the hospital or laboratory. The anti-A serum must be capable of agglutinating the subgroups of A and AB. Checking the blood group by testing the unknown serum against known cells practically assures an accurate blood grouping.

Cross-matching should be done at room temperature and by incubating at 37° C. for half an hour as an aid in detecting agglutinins against such antigens as the Rh factor. Serum used for test tube cross matching should be inactivated to avoid hemolysis which might otherwise give the appearance of a negative reaction. All tests should be checked microscopically as well as macroscopically.

Women who are about to be delivered and who have had babies suffering with erythroblastosis and related syndromes, or who have just been delivered of such babies, will often show abnormal isoagglutinins which may be the cause of serious or fatal reactions unless special precautions are taken in the preparation for transfusion. For this reason all Rh negative pregnant or recently pregnant women should preferably receive Rh negative blood of proper group since the anti-Rh agglutinins may not be detectable in all instances even though the cross-matching is done at 37° C. and followed by centrifugation and examination.

When there is any reason to suspect a transfusion reaction, as in the case of pregnant women recently delivered of babies with erythroblastosis, patients with hemolytic anemia, liver disease, etc., it is well to resort to one of the so-called biological tests. We perform it by administering a 100 c.c. portion of the transfusion and comparing the serum bilirubin of the patient before and five hours after the test dose. If there is no reaction or rise in serum bilirubin beyond the experimental error of the test, it is safe to proceed. Wiener [21] has advocated a similar test which compares the color of the recipient's plasma or serum before and very shortly after the test dose. An increase in the hemoglobin content signifies hemolysis and warns against

completion of the transfusion. No change indicates that it is safe to proceed.

A more crude and not always effective test is simply to administer the transfusion very slowly in which case most reactions will be apparent before too large a quantity of blood is administered.

Plasma, serum and group O donor blood when administered to patients of other groups have been blamed as a cause of hemolytic reactions. The basis of these statements is the theory that the isoagglutinins present in plasma, serum or group O blood may occasionally be of sufficiently high titer [22] to clump and hemolyze the recipient's cells, and thus cause a serious or fatal reaction. Such a sequence of events is theoretically possible. However, the following case previously reported by one of us, suggests that such occurrence is unlikely, or at least, very rare.

A woman, aged 65, weight approximately 45 kilo., was suffering from carcinoma of the sigmoid with blood loss and secondary hypochromic anemia (3,750,000 erythrocytes per cu. mm.). She was given 280 c.c. of group A plasma which agglutinated her cells completely in vitro in a dilution of 1:320. The plasma was administered at the rate of about 6 c.c. per minute. No evidence of agglutination or of incompatible isoagglutinins was found in blood drawn from the opposite arm. The serum bilirubin did not rise above normal.

The adsorption or neutralization of isoagglutinins by the patient's erythrocytes and by dissolved A and B substances present in the plasma [23] does not seem fully to explain the absence of hemolysis in cases of the type reported above. When this patient's whole blood was mixed in vitro with an amount of plasma in proportion to the amount injected, agglutination and hemolysis occurred. A and B substances have been shown to be widely distributed throughout the body in most individuals. The rapid neutralization of isoagglutinins and iso-hemolysins is probably greatly aided by the A and B substances in fixed tissue cells.

The case reported above is not an isolated observation. No hemolytic reactions have been observed in over 4,000 administrations of unmatched plasma in our hospital. Most of this, however, was pooled and consequently had a low isoagglutinin titer. Elliot has had a similar experience using unpooled plasma but this practice is not advisable in view of Aubert's experience.[22]

Certain evidence has recently been put forward to the effect that isoagglutinins in plasma, serum and group O blood may cause hemolysis of the recipient's cells if the titer is sufficiently high. Aubert et al.[22] selected several human sera with an exceptionally high isoagglutinin titer and injected them into recipients of the opposite blood groups. They were able to detect evidence of hemolysis and agglutination in several cases. They noted agglutinates in blood drawn from the opposite arm after the transfusion. They also detected hemoglobinemia and a rise in the serum bilirubin up to 5 mg. per cent. A few recipients showed a drop in the total red cell count and hemoglobin. In this series no serum which had a titer of less than 1:512

produced any evidence of hemolysis. These workers concluded that sera of exceptionally high titer (1:512 or over) might produce hemolysis but that there was no danger from the use of the ordinary pooled material. This very important work should be repeated.

Pollayes and Squillace [24] reported a severe reaction to the intravenous administration of a single dose of commercially prepared lyophile plasma but the facts reported failed entirely to justify the conclusion that the reaction was hemolytic in nature.

It would be of particular importance to determine if there is any increase in the susceptibility to hemolysis in nonsecretors as compared to secretors.

Wiener and Moloney [25] recently reported the case of a woman belonging to group A who received group O blood after a postpartum hemorrhage. The plasma of the group O blood agglutinated the patient's red cells in high dilution. She had a hemolytic reaction but survived. The authors feel that it was the patient's cells that were hemolyzed since the donor's cells could be detected in the woman's blood for some time after the transfusion.

From all the work done to date, it seems justifiable to work on the assumption that serum, plasma or group O blood with an unusually high isoagglutinin titer may cause hemolysis of the susceptible recipient's cell in some instances. These reactions are very rare and can certainly and readily be avoided by pooling serum and plasma. We have never seen a pool of plasma with a higher titer than 1:32 when eight or more bloods were used to make the pool. Levinson and Cronheim,[23] and Davis and Meneely [26] have studied the isoagglutinin titer of pools of serum and plasma and they agree in general that pooled material does not have sufficient isoagglutinin content to be comparable in any way to the serum used by Aubert and his co-workers. More recently, Thalhimer [27] found that the titer of isoagglutinins in unselected pools of normal serum from all groups varied from 1:3 to 1:28. The number of individual sera in each pool varied from 10 to 49. Sophian [28] finds no evidence of hemolytic reaction from the use of plasma, and disagrees with the use of the expression "plasma shock." [29]

When using group O blood, it would seem desirable to be careful to avoid those bloods with excessively high isoagglutinin titers. Witebsky et al.[30] feel that this is unnecessary if purified A and B substances are added to the blood in order to neutralize the isoagglutinins.

Recently Levine and State [31] have stated that dissolved A and B substances in plasma seem to be a cause of reaction when given to patients of the opposite blood group. This would appear to be very unlikely, in view of the experience which we have had with the use of large amounts of unpooled plasma.[32] Elliott also has reported the use of unpooled plasma for several years without reaction.[33] Most of the plasma which we have used, however, has been pooled and the A and B substances presumably have been neutralized, in view of the fact that all pools tested have shown presence of some isoagglutinins.

Allergic Reactions

Allergic reactions are usually attributed to substances of alimentary origin contained in the whole blood, plasma or serum to which the recipient is sensitive. They generally consist of localized urticaria with no systemic reaction. Less frequently, they consist of generalized urticarial manifestations with rise in temperature and occasionally with angioneurotic symptoms. Very rarely, a patient will develop an attack of true bronchial asthma during or after a transfusion of blood, plasma or serum. The possibility of edema of the glottis must be considered, but from all reports on hand, it is probably extremely rare.

It is impossible completely to eliminate these reactions which occur in 0.3 to 1 per cent of transfusions. One way to reduce them is to insist that the blood be obtained from the donor in a fasting condition. However, under ordinary conditions this is a difficult achievement in most institutions. The reactions are seldom severe enough to cause undue alarm and respond readily to epinephrine. True anaphylactic reactions following administration of whole blood, plasma or serum have not been observed by us.

Jaundice Following Transfusion of Whole Blood, Plasma and Serum

Occurrence of jaundice has been reported following the administration of certain yellow fever vaccines containing some human serum,[39] the intravenous administration of human serum [40] and of human whole blood and plasma.[41] The incubation period appears to be one to four months.

No definite etiologic factor has been demonstrated in such cases nor has it been established whether the donors of blood plasma or serum had had jaundice. Likewise, there is no proof of a relationship between the etiologic agent of infective jaundice and hepatitis and the icterogenic agent of blood serum and plasma.

Until more is known on this subject, it seems reasonable to presume that the icterogenic properties of blood and blood derivatives were due to a recent infection of the donor. In view of this, it appears reasonable to recommend that all prospective blood donors should be carefully questioned concerning a history of previous jaundice or contact with jaundice cases. A history of recent jaundice (within six months) or contact with such a case should disqualify a donor for blood transfusion.

Hyperhemolysis Preëxisting in the Patient

Administration of well matched whole blood in patients suffering from hyperhemolysis from all sources but particularly in patients with hemolytic anemia is likely to cause a hemolytic crisis as pointed out by Greppi [34] and Sharpe and Davis.[35] We have observed the death of a patient suffering from hemolytic jaundice following the first transfusion of 500 c.c. of well

matched blood and in several other patients a severe hemolytic crisis. In these cases great care is to be taken to avoid such reactions by testing their "sensitivity" to the whole blood with a token transfusion of 100 c.c. in the manner already outlined. In any case, the rate of administration should be very slow, not to exceed 5 c.c. per minute. This procedure unfortunately is not practical in the newborn. In the icterus gravis neonatorum, extreme care must be exercised and the use of whole blood reserved for cases of extremely severe anemia. The conditions of shock and edema are effectively treated with plasma.

Liver Diseases and Hypoproteinemias

In severe liver damage, particularly if associated with jaundice, and in hypoproteinemias reactions to whole blood transfusion are more common than in the average case. Administration of whole blood should, in these cases, be done at a very slow rate and, in very severe cases, preceded by a test administration of 100 c.c. as already described. Whenever there is no severe anemia, plasma should be used in place of whole blood.

Cardiac Insufficiency

The administration of intravenous fluids, particularly those with high viscosity, such as whole blood, must be done very slowly in all patients with cardiac decompensation. With a rate not exceeding 5 c.c. per min. the danger of overburdening the heart is reasonably reduced to a minimum. The speed of administration in healthy individuals has already been considered.

Other Elements to Be Considered as Possible Causes of Reactions

Administration of small amounts of hemolyzed blood, such as contained in properly preserved blood, is to be considered harmless. As a matter of fact, intravenous administration of large quantities of crystallized or at least purified hemoglobin have been accomplished without apparent damage.[36] Likewise the danger from administration of small quantities of air trapped in tubing, connections and needles has probably been unduly emphasized[37]; however, it should be carefully avoided.[38]

The relatively high potassium content of preserved blood and of plasma prepared from such blood has been pointed out by Scudder[38] as a possible cause of reactions. In practice, however, no reaction has been observed even from administration of several liters of such material.

The administration of even large quantities of cold fluids intravenously does not cause reactions. In view of the fact that severe reactions, however, may follow administration of whole blood, plasma or serum which have been excessively heated, it is desirable to eliminate entirely the practice of warming transfusion fluids prior to administration.

There are some general precautions that greatly assist in reducing the rate of reaction to intravenous fluid therapy. These are briefly:

1. The preparations of crystalloid solution, the collection of blood, the preparation, preservation and administration of plasma, the cleaning assembly and sterilization of apparatus for intravenous fluid administration must be under a single centralized supervision, usually in connection with the clinical laboratory to secure proper standardization and control of each step.

2. A regular system must be instituted for the reporting in detail of all reactions occurring so that critical scrutiny of each case will allow improvement of the service.

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NUTRITION AND RESISTANCE*

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THE subject of nutrition and resistance raises the question of resistance to what—resistance to disease in general, resistance to specific diseases, resistance to therapeutic and toxic effects of drugs, etc. I shall review for you some of the more recent work on nutrition and various types of resistance.

Although it has been generally accepted that good nutrition is a requisite for a maximum degree of resistance to infection, it has been difficult to determine precisely what the relationship might be. It has been repeatedly suggested, for instance, that vitamins A and C are important in maintaining resistance, and the widespread popular acceptance of this idea is attested to by the tremendous quantities of these two vitamins sold each year in the perennial fight against the common cold. Such specific vitamin therapy as a prophylaxis against lowered resistance to infection has as a basis the many reports on vitamin deficiencies in animals and their susceptibility to infection, but convincing proof, especially as concerns human beings, has not been offered.

Thus, in the case of vitamin C, Sigal and King [1] and other investigators have demonstrated protection against the effects of diphtheria toxin afforded to guinea pigs by ample vitamin C intake, although the ability of vitamin C to assist in resisting diphtherial infection in the epidemiologic sense has not been demonstrated. Pinkerton and Bessey [2] found a loss of resistance to murine typhus in riboflavin deficient rats, and Badger, Masunaga, and Wolf [3] reported that thiamine deficient rats have an increased susceptibility to rat leprosy. Wooley and Sebrell [4] recently reported that mice fed less than the minimum requirements of riboflavin or thiamine for normal growth are more susceptible to intranasal inoculation with Pneumococcus type I than mice receiving amounts of these vitamins adequate to support normal growth.

Paired feeding experiments, wherein both the control and experimental groups of mice received the same amounts of food, clearly indicated that the increased susceptibility among the riboflavin-deficient mice was not due to malnutrition following anorexia. The daily administration of riboflavin or thiamine, in amounts five to 10 times that in the control diet, to the mice deficient in these substances at the time of inoculation with Pneumococcus type I, did not reduce the number of deaths.

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Glazebrook and Thomson [5] reported the results of a study of the effects of ascorbic acid administration on resistance to infection in boys living in a large school in England. The work was done in 1938, at a time when distribution and particularly the serving of the food to the 1500 boys (15 to 20 years of age) was poorly managed. It was found that the total daily intake of vitamin C for each boy was only 10 to 15 mg. Urinary tests confirmed the serious degree of vitamin C depletion in these subjects.

The school population was divided into groups and occupied separate tables in the dining hall. Observations were made on the relation of vitamin C to infection by supplying some of the groups with the crystalline vitamin for several months.

The most frequent infections encountered were the "common cold" and "tonsillitis," the latter term being used as an index of hemolytic streptococcal disease of the nose and throat and included sore throat, otitis media, pharyngitis, and cervical adenitis. There was no difference in the incidence of the common cold between the control or vitamin C-treated groups. However, over a six month period, the boys in the control group spent an average of 5.0 days in the infirmary as compared to 2.5 days for the vitamin C-treated group. This difference was due to confinement caused by those infections classified as "tonsillitis," and in the incidence of other illnesses. There were 17 cases of pneumonia and 16 cases of acute rheumatism in the 1100 control boys, and not one case of either disease in the boys given ascorbic acid, though it should be pointed out that the control group had three times the number of subjects of the group given ascorbic acid.

This group of boys must represent a unique case since most studies of the general population indicate a much higher level of vitamin C intake than 15 to 20 mg. The results do not, therefore, justify ascorbic acid therapy in those already receiving "accepted" requirements. In fact, in a later communication, Glazebrook [6] emphasizes that these results must not be interpreted to mean that vitamin C plays a major rôle in resistance to disease.

Undoubtedly there is a wide variation in the "susceptibility" to hypovitaminosis C among individuals. Thus scurvy may first be indicated by a gingivitis, conditioned by local tissue susceptibility and improper oral hygiene. Likewise, anemia may be an early sign of scurvy, but it is conditioned by simultaneous suboptimal intake of iron. Thus, the individual with a latent vitamin C deficiency is placed in a precarious position against the attack of other disease-precipitating factors.

These considerations are undoubtedly important in interpreting the apparent conflict between the experiment of Crandon, Lund, and Dill [7] and the many reports on scurvy from other parts of the world. In the self-imposed scurvy produced in Crandon, the intake of other dietary factors was adequate and the subject was not exposed to other extraordinary natural conditions. Under these circumstances a great deficiency of vitamin C was required to produce certain signs of scurvy. Physical signs often associated with naturally-occurring scurvy, which may exist with less severe de-

ficiency of the vitamin, are undoubtedly precipitated by a variety of other conditions not experienced in the more controlled experiment.

Since it cannot be denied that some of our people are subsisting on inadequate diets, including low ascorbic acid intakes, these considerations and particularly the positive results of Glazebrook and Thomson require attention by health authorities in their efforts to prevent or lessen the disability caused by infectious diseases.

A recently reported investigation [8] on approximately 300 college students at the University of Minnesota showed no indication that either large doses of vitamin C alone or large doses of vitamins A, D, C, thiamine, riboflavin, and nicotinic acid together have any important effect on the number of infections of the upper respiratory tract when administered to young adults who presumably are already on a reasonably adequate diet. No nutritional studies were made but it seems reasonable to assume that these American college students were receiving a far better diet than the English boys reported in the previous study.

Reports on the relation of nutrition and resistance to disease are not confined to the effect of vitamin deficiencies. A recent report by Sako [9] presents investigations on the relation of protein, fat, and carbohydrate to "resistance to infection." In this study, young albino mice were fed diets varying in their content of protein, fat, and carbohydrate but with identical vitamin supplements. Growth on these diets was subnormal as compared with a stock diet, and growth on the low protein diets particularly was practically nil. After six weeks, the animals were injected with a standard multiple lethal dose of pneumococci and their survival time noted. Animals fed the high protein special diets survived longest; those fed the low protein diets died most quickly.

Dr. Paul Cannon [10] in his presidential address before the last meeting of the Association of Immunologists reviewed the importance of dietary protein for antibody formation. Cannon has shown experimentally that rabbits whose protein reserves had been reduced by low protein diets have a distinctly subnormal capacity to produce specific antibodies. This is in accord with evidence covering the increased susceptibility to infectious diseases observed along with inadequate diet during World War I. There is considerable evidence that an adequate dietary source of protein is of major importance in maintaining a high resistance, and it is appropriate to mention that the main protein foods are also the best sources of minerals and vitamins.

Somewhat in contrast with the work so far mentioned is the report of Feller, Roberts, Ralli, and Francis [11] in a different type of investigation on human beings in which they failed to demonstrate that vitamins A and C had any influence on: (1) the capacity of nasal secretions to inactivate influenza virus; (2) the titer in serum of neutralizing antibodies for influenza virus; (3) the activity of lysozyme in nasal secretions; (4) the titer of com-

plement in blood serum; or (5) the phagocytic activity of polymorphonuclear neutrophilic leukocytes for pneumococci. These studies were performed on normal human beings with diets adequate in calories and all foodstuffs except either vitamin A or C.

It is not possible to conclude, of course, that because these five immunologic phenomena were not influenced by changes in the blood plasma concentrations of the vitamins or by the degrees of deficiency attained, that vitamins A and C are not concerned with maintaining resistance to infection. However, these purely negative responses do emphasize the necessity for guarding against acceptance of a general conclusion that vitamins A and C have a specific function in "resistance to infection," particularly when the diet is adequate in other respects.

Changing the subject rather abruptly I should like to read part of an autopsy report[12]: ". . . arterial lesions consist of focal to extensive calcification, less often hyalinization or necrosis. These lesions were found in the lungs, heart, kidney, pancreas, thyroid, stomach, intestines, and mediastinum. Hyalin necrosis of skeletal muscle with or without calcification was found in all locations thus far examined. Lesions of the heart consist of necrosis of muscle followed by the formation of loose sparsely cellular scars. Slight to marked bone marrow aplasia (of granulocytes) was observed."

That is not an autopsy report of an elderly individual who died from the effects of a number of degenerative diseases, but of a young rat fed a diet adequate in all known nutrients but to which 1 per cent sulfaguanidine had been added to the ration. The above mentioned changes are completely prevented if yeast or liver is included in the diet. It is probable that sulfaguanidine inhibits the growth of certain intestinal bacteria which normally synthesize essential unidentified nutrients presumably belonging to the vitamin B-complex.

Intestinal bacteria are apparently of considerable importance to the nutrition of animals and of human beings. It is well known that vitamin K is synthesized by bacteria in the intestinal tract in quantities sufficient normally to meet the needs of man and most animals. Biotin, one of the vitamins of the B-complex, is provided to man in larger quantities by intestinal bacteria than by the diet.[13] Man may not develop deficiencies of biotin, pantothenic acid, pyridoxine, and other essential nutrients because these substances are made for him by microörganisms in the intestinal tract. But should the intestinal flora be altered, as by administration of drugs, diseases primarily nutritional in etiology may result.

We have been studying the relation of nutrition to the tolerance of daily administration of one of the synthetic antimalarial drugs. Experimentally in the rat, with carefully controlled purified diets furnishing good nutrition, we have not observed any remarkable pathologic changes. With the growing rat, daily administration of this drug inhibits growth. The extent of in-

hibition depends upon the amount of drug and the adequacy of the diet. Inhibition of growth due to the drug is additive to growth inhibition due to lack of certain essential nutrients. Thus, an animal on a diet partially deficient in riboflavin does not have a normal growth rate. If the drug is added to this partially deficient diet, its toxic effect is superimposed on the already ill effects of an inadequate nutritional state, and the animal is, therefore, in a more precarious position. Improvement of the diet by furnishing a normal amount of riboflavin will result in better growth but it will not prevent the growth inhibition due to the drug. It is probable that the same effect will be found with diets partially deficient in other nutrients. Therefore, because the toxic manifestation of the drug is additive to the effects of inadequate nutrition, it seems apparent that a good nutritional status, and an adequate nutritional intake, are important in tolerance to continued administration of certain drugs.

In summary, it may be stated that the diverse nature of the investigations on nutrition and resistance strongly favors a general conclusion, and a positive conclusion. The multiplicity of nutritive factors and pathogenic agencies used in the various studies suggests that a deficiency of any one of several nutrients may lead to a state of generally lowered resistance without any one factor bearing a so-called "specific" function. Many investigators have referred to the nonspecific nature of their findings. Certainly the experiments do not offer a rational basis for "overdose" therapy with any particular dietary factor, but they do justify accepting a strong relationship between nutritional well being and general resistance. And it is well to emphasize that nutritional well being is best obtained by an intelligent selection of foods of high nutritive value. The intelligent selection of foods of high nutritive value, so as to obtain in a quantitative manner a daily diet which really supplies the many nutrients necessary for good nutrition, cannot be left to the discretion of the average patient. Specific and accurate nutritional therapy should be a vital part of every physician's armamentarium.

Note. Since this address was given two interesting papers have appeared concerning nutrition and resistance. Trager [14] has reported that the blood level of biotin, one of the members of the vitamin B-complex, greatly influences the severity of avian malarial infection. Biotin-deficient chickens and ducks inoculated with large doses of *Plasmodium lophurae* showed peak parasite numbers 50 to 100 per cent higher than controls. The increased susceptibility in the biotin-deficient animals was not correlated with any general weakness resulting from the biotin deficiency. Older chickens which are more resistant to malarial infection showed a higher level of biotin in the blood than more susceptible younger chickens.

Smith, Lillie, and Stohlman [15] have studied the influence of dietary protein on the toxic effects of azobenzene, p-aminoazobenzene, and p-dimethylaminoazobenzene in rats. The degenerative liver changes and consequent impairment of liver function produced by these azobenzene compounds

are preventable by feeding high levels of good quality protein, particularly casein.

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PSYCHOSOMATIC ILLNESSES IN URBAN PRACTICE *

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PSYCHONEUROSES with their attendant autonomic alterations of visceral functions frequently assume the pattern of organic disease and become major problems in identification and management. When they are associated with frank morbid anatomical processes they create confusion in diagnosis and often lessen the effectiveness of therapy. Economically, their significance is not generally recognized, although if valid statistics were available they would rank high among the causes of inefficiency and days lost from employment, to say nothing of the added cost of medical care. One patient for 10 years set aside 50 dollars a month from a small income for medical services, and the drug bill of another amounted to 25 per cent of her monthly salary. They are responsible for a large number of rejections of selectees for military service and constitute a considerable percentage of patients in base hospitals at the present time. They vitally affect every phase of our social life.

Physicians looking for "real pathology" are apt either to overlook the significance of psychosomatic complaints or to be impressed with the apparent futility of trying to effect a cure. However, more interest is being shown by medical and social agencies now than ever before in the identification of their causes and management of treatment. This interest has been stimulated by the general advance of medical science, better preparation of medical students, better teaching in medical schools, and by the increased public interest in making responsible medical care available to all classes of society. We hear and read more about treating the individual and not the disease; about the contrast between viewing the patient as an entity and the individual with some specific form of disease. And as society is thrust upon the threshold of an era of increased social responsibility that must be shared by the whole social order, religion, science, business enterprise, and government, it will become increasingly obvious to the public how vitally social and economic problems affect the individual's well-being and how much bodily pain and metal anguish may be caused by their wrong evaluation. We may then, as clinicians, frankly accord to psychopathology the same importance given to organic pathology in alterations of physiological functions common to both conditions.

Psychosomatic disturbances are no respecters of persons. They affect the high and the low, the rich and the poor, and the sick and the well. They have their origin, unquestionably, in inherited and acquired traits. The age

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incidence of episodes is from the time of early self-determination to death. No race or sex is immune and the influences of party or creed are negligible. The specific etiologic factor appears to be a virus of inadequacy adapted to the human race from its beginning. It is spread by contact and fomites of commonplace intellectual and emotional practices.

The effect of the virus is upon the central nervous system, and somatic symptoms appear with the involvement of the autonomic portion. However complicated its connections may become, the reflex arc in one form or another is the physiological unit which forms the basis of most, if not all, nervous activity. The centers of such complex phenomena as consciousness, intelligence, judgment, memory, speech, and other phases of symbolic thought, of which little is known, lie within the aggregations of cells constituting the cerebral cortex where reflex action may still be simple enough to be analyzed, as in the case of conditioned reflexes, or so complicated as to be lost in the maze of human behavior. There are direct paths leading from this mantle of consciousness to the midportions of the brain where are located the autonomic centers with control over elemental functions which respond directly to cortical stimuli.

Patterns of thought and autonomic response are fashioned in early life and become more inflexible with the passing years. Into these molds are poured the ideas and experiences that form the personality society recognizes. The effect of psychic trauma upon these patterns will depend upon their degree of flexibility and upon the nature and amount of the casting material. The manifestations of trauma are manifold. They may be behavioristic or somatic or both. The symptoms are variable, transient or prolonged. The physiological reactions to fright may be present in any form whether due to fear of body harm or to anxiety from any cause. With the conditioning of time they may not be obvious except in acute exacerbations. Somatic symptoms may vary from transient elevation or lowering of arterial pressure to complex manifestations of aberrant physiological processes that constitute definite clinical syndromes. Sometimes a single organ system is involved and at other times a number may be affected. The circulatory and alimentary systems frequently present the most annoying symptoms. Tachycardia, extrasystoles, and alterations in blood pressure are the most common cardiovascular symptoms. Dysphagia, anorexia, distention, nausea and vomiting, hyperchlorhydria, pain and tenderness in the epigastrium or moving from place to place in the abdomen, constipation or diarrhea, mucous colitis and the "spastic colon" are gastrointestinal symptoms.

The respiratory rate may be quickened. There may be dyspnea on exertion, smothering sensations, or frank attacks of bronchial asthma. An interesting phenomenon in respiratory tract involvement is the quickened deep breathing that leads to hyperventilation and its attendant feelings of dizziness, faintness, and unreality. These sensations can readily be demonstrated to the patient when he is recounting his experiences by having him breathe deeply and frequently by the watch.

The genitourinary symptoms include increased or decreased libido, impotence, dysuria, frequency, perineal and lower abdominal and lumbar aches and pains.

Altered functions of the ductless glands may be indicated by prolongation of the menstrual cycle, missed periods, overactivity sometimes with hyperplasia of the thyroid gland and alterations of the blood sugar curve.

The most frequently observed cutaneous manifestation is simple erythema. Increased response to intradermal tests for allergy and especially to histamine often causes confusion in diagnostic procedures.

Frank nervous symptoms may arise from the upper or lower segments of the nervous system. Peripheral nerve pain, paresthesias, anesthesias, hyperesthesias of the skin are common. From the higher centers come the signs of hypersensitivity to suggestion and unusual awareness of visceral activity, as the heart beat and peristaltic movements of the gastrointestinal tract. Headache, fatigability, restlessness, and sleeplessness are among the earliest complaints, and then follow the travails of indecision, poor judgment, faulty memory, etc., as parts of the phenomena of psychic disorder.

Psychosomatic symptoms may appear as an anaphylactic phenomenon in emotional shock. They occur also as manifestations of repeated, less severe psychic traumas. It is interesting to note how often an individual pattern is presented. In one individual the blow is felt upon the gastrointestinal tract, in another the cutaneous nerves bear the onus, in another the ductless glands, in another the circulatory system in the form of extrasystoles or hypertension, and in another if the patient suffers from bronchial asthma, acute exacerbations may be precipitated at a time when specific therapy should have controlled the paroxysm. A familial tendency is also occasionally observed. A young woman whose chief complaint was frequency of urination, voiding once or twice an hour during the day, stated in her family history that her father and three brothers were "nervous" and had "kidney trouble."

The prognosis in these cases depends upon the severity and duration of the illness. Transient symptoms of emotional shock where the cause is obvious respond readily to treatment. The prolongation of symptoms and their interpretation as evidence of organic disease may fix them in the consciousness of the patient. In some instances the purely psychic symptoms may be relatively few and obscured by localized complaints as pain over McBurney's point, dyspepsia, constipation, etc. Then the essential causative factors may be most difficult to determine. With the passing of time, the individual tends to make more involved adjustments on the basis of his inadequacy and chronic invalidism may result.

Resistance to the disease varies with and within the individual. The defense mechanism involved is analogous to the mechanism giving us acquired immunity to infections. Acquired immunity to infectious disease is produced by the body's response to repeated subclinical irritations or by a sustained effort which eventually overcomes an infection and establishes a

defense against microbial invasion. For a short period in early life the mother's immunity protects her child, during which time normal parasites take up their abode upon and within the infant's body. The colon bacillus flourishes in the alimentary canal, the staphylococcus upon the skin, and the streptococcus in the oral cavity. Kept within proper confines, they cause no harm and a communal relationship is established between parasites and host. Repeated minor invasions of the staphylococcus build up an increased resistance of the body against the time when an injury may allow a large number of these organisms to enter its tissues. The colon bacillus frequently invades the urinary tract. Filtrable viruses injure the mucous membranes of the nasopharynx allowing the organisms of the mouth to produce the common upper respiratory infections. These minor infections condition the body for future invasions of larger numbers or more virulent bacteria. As in all natural defense phenomena the conditioning process is variable and unpredictable.

Likewise, in the realm of social experiences, maternal influence protects the child. Later, by repeated contacts at home and school, at work and play, in making a living or making of friends, throughout life, the impact of human relations enhances or impairs the effective life of the individual. Lasting immunity may ensue from devastating personal experiences but, in the main, if we live out our life expectancy, our happiness and usefulness depend upon a varying state of immunity or hypersensitivity to the impacts of every day living. As with somatic infections, the outcome of each episode will depend upon the number and character of the impacts and the individual's resistance to them. Wherever the blows may fall, and whatever the complexes may be, the symptoms express an exaggerated normal reaction to fear. Some reactions of childhood may persist throughout life, and others result from experiences of the present or immediate past. Upon their conditioning depends the body's response to the intrusion of deleterious influences.

No doubt the most important influence shaping the child's pattern of response is parental example. Guidance by church and school stands little chance of being effective in homes torn by dissension or controversy about the child's behavior. Later experiences in love and plans for a career place upon many unprepared shoulders heavy weights of responsibility. The effect of indecision, of inordinate ambition in adolescence, may be felt for years afterward. Religious experiences, business and professional associations, family cares and marital incompatibility, physical handicaps, and social delinquencies are commonplace contributing factors in adult life to the development of feelings of inadequacy and symptoms of autonomic nervous system imbalance. In order to determine the nature and seriousness of these influences, considerable understanding, time, and patience are required. The attitude and preparation of the first physician to prescribe for the physical manifestations of stresses will greatly influence their outcome. If he is unaware of psychic factors involved, or, for any reason, fails to

enlighten his patient about the nature of his complaints and directs his attention solely to the amelioration of presenting symptoms, fear of sickness and death may be added to an already burdened mind. Mention of findings such as a heart murmur, a two plus Wassermann, questionable peptic ulcer, or a retroflexed uterus, may be taken to heart and accepted as evidence of the physician's desire gently to break the news of impending disaster. From such fears arise some of the most painful anxiety states which may be made worse by unnecessary, even though well-intentioned, medical or surgical treatment.

Clinically, these patients can be placed in three empirical groups:

First—the acute exogenous group. Individuals who suffer from stresses that would properly place burdens upon right-thinking persons, as the concern of a sick mother for a wayward son, the sudden awakening of a man to the hazards of a new undertaking, broken love affairs, and the sudden facing of major health problems.

Second—the social welfare group. Individuals whose difficulties are due to repeated or constant friction in home, business, and social affairs.

Third—the personal habit group. Individuals whose faulty habits of thinking and behavior cause them to feel inadequate for normal social and business life, including abnormal sex practices, excessive use of alcohol, drug and prescription addicts.

The problems of the first group present little difficulty in diagnosis and, with the proper appreciation of causes, are amenable to sympathetically administered palliatives and the assistance of family and friends.

In the second group constituting a large number with prolonged symptoms, it becomes necessary to secure more information than can be obtained from the patient for the identification of offending circumstances. Not infrequently the conduct of other members of the family or poorly advised business associates needs more attention than does the patient. Here the physician may find himself confronted with a problem for which he has little time or preparation, and it is with this group that the trained social worker can render the most assistance in diagnosis and treatment. Many are borderline psychiatric cases.

The third group demands psychiatric skill well recognized in modern medical practice.

Treatment of the first two groups includes psychotherapy, medical treatment, and prophylaxis. Whether the general practitioner or the specialist in any branch of medicine desires to, or not, he has to accept responsibility for the identification of psychosomatic disturbances and their management, personally or by reference. Care and time spent in history taking prevent many headaches in evaluating physical findings. The patient with psychosomatic symptoms unrelated to organic pathology usually will give an involved history if permitted to do so, although specific complaints may be the only ones brought out at the first visit to the physician. Therefore, an hour or more

given over to the patient's recital without direct questioning may not be wasted and will save valuable time and unnecessary reëxaminations later. Physical examination necessarily must be carried out according to the problem presented with full appreciation that physiological alterations caused by psychic disturbances produce discomfitures, and that the patient may not be telling a falsehood when he states he has a pain in his epigastrium, numbness of his extremities, or dyspnea on exertion, even though there may exist no morbid process to account for these symptoms. Remedial measures other than conversation are best withheld until a degree of harmony between history and physical findings can be established in the minds of patient and physician regardless of time consumed. When symptoms occur to complicate somatic disease, strict attention to obvious pathologic lesions until their cause may be ascertained, will obviate much difficulty later. The effect of sedatives may be likened to that of opiates administered to a patient with a questionable surgical abdomen, and the resulting hazards in diagnosis and treatment are frequently as comparable. In fact, any medicine given before the nature of the illness is known may give the patient a false sense of security and lead him to believe or hope that his illness may be primarily attributable to some physical cause.

Inasmuch as many symptoms are associated with such obvious physiological abnormalities as hyperchlorhydria, hypo- or hyperthyroid activity, abnormal glucose tolerance curves, spasticity of the gastrointestinal tract or altered arterial pressure, the question naturally often arises about what medicinal or other therapeutic measures are indicated for the alleviation of such conditions. When it can be made plain to the patient that it is to his interest to remove the cause of his trouble, it does not matter much what crutches are used if they are not allowed to become habit forming, or the means by which he may punish himself for his lapses. Basal metabolic rates will return to normal, blood sugar alterations will disappear, and the colon will lose its spasticity as he gets his balance and faces the world with more poise and confidence. In well developed cases he must learn to expect relapses, and, until he can make a total adjustment, he must be satisfied if they recur less frequently and are of shorter duration. On the other hand, patients with confirmed psychosomatic disease may become ill with essential hypertension, renal colic, coronary disease, peptic ulcer, frank mental disease, and all other physical afflictions common to man. Likewise, prolonged illnesses may be complicated by emotional stresses and their accompanying trains of psychosomatic symptoms.

I believe most psychiatrists are of the opinion that many, if not most, of the cases of the first and second group, if properly handled, will fare better in the hands of the family physician than in their own. Certainly in the majority of instances the individual simply needs the doctor's moral support for a period of time, with the minimum of therapy, or material assistance from sources prepared to give it. Many cases, however, do become psychiatric problems, especially where diagnosis and treatment at the hands of

their physician have shown lack of appreciation of factual causes. The frequent necessity of adapting a patient's personal life to strictly somatic illnesses unquestionably accounts for many failures to recognize and properly care for psychosomatic disturbances. There is, however, little question but what the medical profession has often erred in considering the patient the doctor's property, and has extended the patient-physician relationship to the point where mysticism born of wishful thinking has been substituted for the realistic approach of scientific medicine. We may admit our responsibility for much unscientific rationalizing that has impeded the progress of medicine and frequently evoked the scorn of our critics. One factor in unscientific rationalizing is the difficulty of obtaining valid social histories from individuals who are loath to see any connection between psychic stresses and physical discomfitures when perhaps the causes of the stress are commonplace practices or occurrences for which many of their acquaintances appear to find satisfactory compensations. Another source of error lies in the exploitation by laity and profession of tonics, sedatives, hormones, and vitamins as panaceas for emotional disturbances, and the unwarranted assumption that physical fitness, especially in relation to the ductless glands, insures emotional stability. We deal with human beings, not tokens of scientific, economic, or social progress. And in the pursuit of truth, the human mind has not invariably passed by graded steps from witchcraft to metaphysics, and from metaphysics to science, but has grudgingly accepted, by the painful process of trial and error, every new contribution made for human betterment. Moreover, many individuals appear to be unable to accept these contributions and at the same time realize that they follow, and do not invalidate, the natural laws shaping human progress.

Lack of time and training frequently renders the physician's task of determining the source or solution of the patient's troubles very difficult. When they arise entirely, or in part, from misfortune or ineptitude in daily living and faulty family adjustments, social agencies in the larger cities are equipped to assist by making investigations and recommendations the physician cannot undertake. The fact that these agencies accept responsibility often has a very salutary effect upon disturbing elements in certain cases.

Each physician should have his own manner of approach after having determined something of the nature of contributing causes. Confidence in his own ability and forthright interest in the patient's welfare can ordinarily be demonstrated in the same manner in which he would refer a patient to a surgeon, internist, or orthopedist. But to the lay mind these illnesses often bear a stigma more distasteful or fearful than did cancer, syphilis, or tuberculosis, three decades ago. Therefore, patience, and not abruptness, sympathy, or disgust, should keynote the physician's advice and the patient should be made to understand what benefits might be expected from such reference. Much might be said about the manner in which cases needing the attention of psychiatrist or social agency can be brought to want the assistance they provide.

The importance of prophylactic measures has been given little direct attention except in the field of child psychology; yet it should be obvious to any interested observer that although a pattern may be formed in childhood, it does not follow that childhood experiences necessarily account for all emotional disturbances developing in adult life. We find sources of disturbances in every field of human endeavor, and if we in this democracy are to fulfill the obligation we believe is ours, to produce not human robots or intellectual frankensteins, but confident, clear thinking, free men and women, we must, in this period of the world's history, coördinate all our efforts in church, business enterprise, science, and government, not alone to salvage human waste, but to safeguard the ideals we profess. Only the physician is in position to accept responsibility for the individual as a biological entity in a social world in matters pertaining to his physical and mental health, but in the broader sense illnesses of all kinds are community and public health problems.

Increasing emphasis upon the validity of diagnostic criteria and upon the axiom of proved medical practice, i.e., to remove the cause is to effect a cure, demands, where possible, closer coöperation of the medical profession and social agencies. We may then apply the same interest in determining specific causes for psychosomatic complaints as is shown in the identification of febrile illnesses, heart disease, or the evaluation of symptoms of the surgical abdomen, and to institute suitable measures of relief for the cases in which major social problems are involved. We may be able, also, better to evaluate the factors in our national economy contributing to their production.

THE EFFECTS OF NOVOCAIN INJECTIONS ON SIMULATED VISCERAL PAIN *

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PERIPHERAL manifestations of nerve root involvement in spondylitis have been known since the days of von Bechterew,[1] but it was not recognized until many years later that similarly radicular pain secondary to hypertrophic or infectious arthritis of the spine [2, 3, 4, 5, 6] or narrowing of the intervertebral spaces [7, 8] could mimic intrathoracic disease or acute abdominal emergencies. The usual treatment of this type of pain has consisted of various drugs, physical measures including baking and massage, manipulations of the affected joints, and often roentgen-ray therapy. Unfortunately most of these measures yield but transient relief and frequently the pain has persisted or recurred soon after treatment was stopped. For these reasons it has been thought worth while to try the effects of novocain injections on a group of patients in whom pain simulating visceral disease was the result of paravertebral muscle involvement, secondary to spondylitis.

Local or regional injection therapy for muscle pain is not new. Its origin has been traced back to the time of the Tsin period about 300 A.D.[9] Since then the beneficial effects of injection of many substances into varying locations for the relief of low back pain and sciatica have been described. Kellgren [10, 11, 12, 13, 14] first demonstrated that in a certain number of patients with simulated visceral pain, pressure over the paraspinal muscles adjacent to a localized kyphosis reproduced the pain and injection of large amounts of 1 per cent novocain into this area abolished the symptoms for varying periods of time. Similar observations have been reported by Harman and Young [15] in patients with "rheumatic" lesions of the deep back muscles but no spinal involvement.

During the past two years 26 patients with spondylitis and simulated visceral pain, in whom the symptomatology could be reproduced by pressure on the muscles lateral to one or more vertebrae and by torsion or hyperextension of the spine at the same level, were subjected to a similar procedure. The cases fell readily into groups:

1. Those with simulated visceral pain and no organic visceral disease.
2. A larger group with visceral disease and simulated visceral pain due to somatic disease.

In the first group, symptoms frequently were referred to the abdomen, often "renal colic," although "pseudo-angina" was also encountered. Clinical and laboratory studies always failed to reveal organic visceral disease, but all patients displayed the characteristic findings: tenderness immediately

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lateral to one, two, or three dorsal or lumbar vertebrae, reproduction of the abdominal or thoracic complaint on pressure at these sites and on forced motion of the spine, and radiographic evidence of a spondylitis at the same level.

The second group was composed chiefly of patients with organic heart disease and "pseudo-angina." Many had been followed for years with anginal symptoms believed due to the cardiac disease but with no response to the usual therapeutic measures. Points of tenderness to the left of the lower cervical and upper and mid-dorsal spine were always present and pressure and manipulation at these sites reproduced exactly the "anginal syndrome." Radiographically, hypertrophic changes in the vertebrae were observed, except in those patients with rheumatic fever and acute or subacute spinal involvement. A negative roentgenogram does not, however, preclude the diagnosis of spondylitis. Parker and Adson [16] have shown pathologically that hypertrophic changes resulting in cord compression may exist for a considerable period of time without their radiographic recognition.

Case Reports

The following cases are illustrative of group 1.

Case 1. R. N., a 46 year old female, stated that for six months prior to admission she had suffered from intermittent episodes of severe, sharp precordial pain frequently radiating into the left arm and usually occurring after heavy exertion. There was no clinical or laboratory evidence of cardiovascular disease. Marked muscle tenderness immediately to the left of the bodies of the ninth and eleventh dorsal vertebrae was elicited and pressure at these sites reproduced exactly the spontaneous pain. Neurologically, hyperesthesia to pinprick from D9 to D12 was present on the left posteriorly and over the anterior left hemithorax. The left breast was markedly tender on pressure. Radiographic examination showed a moderate degree of hypertrophic spondylitis.

Eight c.c. of 2 per cent novocain were injected at each of the two tender sites and about two hours after the injection the pain was completely gone. The following day neither the hyperesthesia nor breast tenderness was present and the patient stated that for the first time in six months she had been able to sleep on the left side and not awaken due to paroxysms of pain. She was still free from pain 11 months after the injection.

Case 2. M. N., a 54 year old female, for three months prior to admission suffered from steady severe low-back pain radiating down the buttocks. During the preceding week she had experienced three attacks of severe right loin pain radiating anteriorly and downward into the groin. These were believed by her physician to be renal colic and each required several injections of morphine for relief. Because of this she was admitted to the hospital for urological investigation. Examination revealed tenderness to the right of the first lumbar vertebra and over both sacroiliac synchondroses. Pressure and forced motion at the lumbar site produced pain similar to the previous acute "renal colic," and pressure over the sacroiliac articulations caused severe low-back pain radiating down the buttocks. Ankle jerks were absent and there was decreased sensation to pinprick of the lower extremities from the knees down. The urine was negative and urological investigation revealed no evidence of urinary tract disease. Roentgenogram of the spine showed an advanced degree of

hypertrophic spondylitis of the dorsal vertebrae and slight changes in the lumbar region.

Ten c.c. of 2 per cent novocain were injected into the paravertebral muscles to the right of the first lumbar vertebra and 15 c.c. at the upper margin of each sacroiliac joint. The following day she was markedly improved. On the second day she felt even better, no longer experiencing pain on changing from the recumbent to the sitting position nor on walking. There was no further radiation of pain anteriorly. Eight months after injection, she was free from all pain and had had no further episodes of "renal colic."

The following cases illustrate results achieved in group 2.

Case 1. S. M., a 60 year old female with known hypertension and hypertensive heart disease for seven years and thyrotoxicosis of three years' duration, complained of sharp, intermittent, knifelike pain in the lower left anterior chest for the past two months. These had been considered anginal in nature but had not been relieved by nitroglycerine. Examination revealed typical findings of hyperthyroidism and hypertensive heart disease with auricular fibrillation. On pressure immediately to the left of the second, third and fourth dorsal vertebrae and on torsion of the spine the "anginal" symptoms were exactly reproduced. Hyperesthesia to pinprick was present over the left hemithorax and the left breast was moderately tender to pressure. Radiographic examination of the spine revealed moderate hypertrophic changes with lipping and beaking along the anterior aspects of the bodies plus a slight scoliosis from the second to the fifth dorsal vertebrae.

Eight c.c. of 2 per cent novocain were injected into the paravertebral muscles to the left of the second, third and fourth dorsal vertebrae. The following day there was definite improvement with the "anginal" pain much less frequent and severe. By the second day the pain had completely disappeared and could no longer be reproduced by similar pressure or motion of the spine.

One month later she complained of pain in the lower back radiating anteriorly. There was exquisite tenderness with reproduction of the pain at two points over the left lumbo-sacral articulation. At each site 6 c.c. of 2 per cent novocain were injected and by the second day all pain had disappeared. There had been no recurrence of either pain 12 and 11 months respectively after injection.

Case 2. E. K., a 27 year old female with known rheumatic heart disease since the age of 15, complained of sharp intermittent pain under the left breast radiating posteriorly and accompanied by palpitation for the previous three months. Examination showed rheumatic heart disease with mitral insufficiency and stenosis and aortic insufficiency, auricular fibrillation and mild congestive failure. The blood pressure was 126 mm. Hg systolic and 50 mm. diastolic. The clinical status and laboratory data indicated that she had active rheumatic fever. The pain originally was believed due to the aortic insufficiency but nitroglycerine afforded no relief. Careful examination of the spine revealed that on pressure just to the left of the sixth dorsal vertebra the pain was reproduced and even exaggerated. There was diminished sensation to light touch and pinprick over the left chest anteriorly down to the sixth intercostal space and posteriorly down to the level of the fourth dorsal vertebra. Roentgenogram of the spine was normal.

At the point of tenderness 7 c.c. of 2 per cent novocain were injected into the deep paravertebral muscles with almost immediate disappearance of pain. For the subsequent nine months she was completely free from all pain and then she experienced a recurrence similar to the initial episode. At this time there was tenderness with reproduction of the complaint on pressure to the left of the first, second and fourth dorsal vertebrae. Six c.c. were injected into each of these areas and the pain was completely relieved within two hours. There had been no recurrence three months later.

Results

All patients injected were relieved of their pain. Many were followed for over a year after injection with no recurrence. Several had a recurrence of symptoms from six to eight months later at which time the procedure was repeated and prompt relief was obtained. Frequently relief occurred within

Table I

Paravertebral Muscles

Muscle	Extent and Possible Level of Injection	Nerve Supply
First Layer		
Trapezius	C7–D12	External branch of spinal accessory nerve Anterior primary divisions C(2), 3, 4
Latissimus Dorsi	D6–Sacrum	Thoracodorsal nerve (C5–8 of brachial plexus)
Second Layer		
Rhomboideus		
Major	C7, D1	Dorsal scapular nerve (chiefly anterior primary
Minor	D1–4(5)	division C5 of brachial plexus)
Serratus Posterior Superior	C7–D2(3)	Anterior primary divisions D1–4 = intercostal nerves
Serratus Posterior Inferior	D11–L2(3)	Posterior primary divisions C2–4 (C1, 5, 6)
Third Layer		
Sacrospinalis (Erector spinae)	L1–5	Posterior primary divisions L1–5
Iliocostalis		
Cervicis	C4–D7	Posterior primary divisions C8–L1
Dorsi	C7–D12	
Lumborum	D5(6)–L5	
Longissimus		
Capitis	C(5)6–D3(4)	Posterior primary divisions C1–L5
Cervicis	C2–D4(5, 6)	
Dorsi	D1–L5	
Spinalis		
Cervicis	C2–D2	Posterior primary divisions lower C
Dorsi	D2(3)–L2	D6–9
Semispinalis		Posterior primary divisions
Capitis	C3–D6	C1–4(5)
Cervicis	C2–D5	C3–6
Dorsi	C7–D10(12)	D3–6
Multifidus	C2–Sacrum	Posterior primary divisions C1–L3

10 minutes after injection but at times one to two hours elapsed before an effect was evident. In no case did a frank failure result. Three cases experienced only a moderate degree of relief following injection but on repetition of the procedure seven to 10 days later complete and permanent relief was obtained.

A not infrequent secondary effect was transient burning and superficial tenderness at the sites of injection apparently due to the muscle and subcutaneous infiltration. This always disappeared within eight to 12 hours. Thereafter, spontaneous pain was absent and pressure and manipulation of the spine at the site of injection could no longer precipitate it. The larger amount of novocain seems to have been no more effective than the lesser. In 56 injections given to 26 patients no complications occurred. At all times an attempt was made to eliminate the psychic effect of a new form of therapy in patients with chronic disease. The patients were never promised a therapeutic success and the element of suggestive therapy seems to have played little part in the end result. In several cases in which normal saline was injected instead of novocain, the pain was relieved for 12 to 24 hours but thereafter returned with its original intensity and distribution.

Discussion

The mechanism of the radicular syndrome occurring in association with arthritic changes in the spine has been ascribed to an irritative process involving the nerve roots at their exit through the intervertebral foramina, either a proliferative bony compression,[3, 4, 5, 6] primary narrowing of the foramina,[7, 8] or soft tissue changes.[17] Inasmuch as the motor nerves also

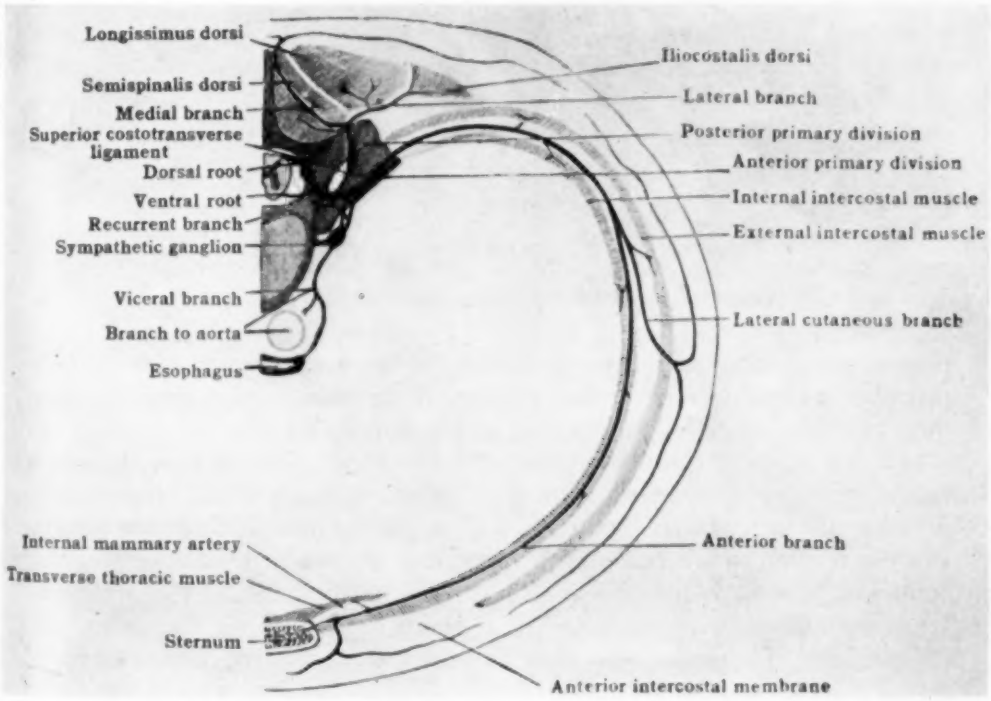

Fig. 1. Diagram of the distribution of a typical thoracic nerve.

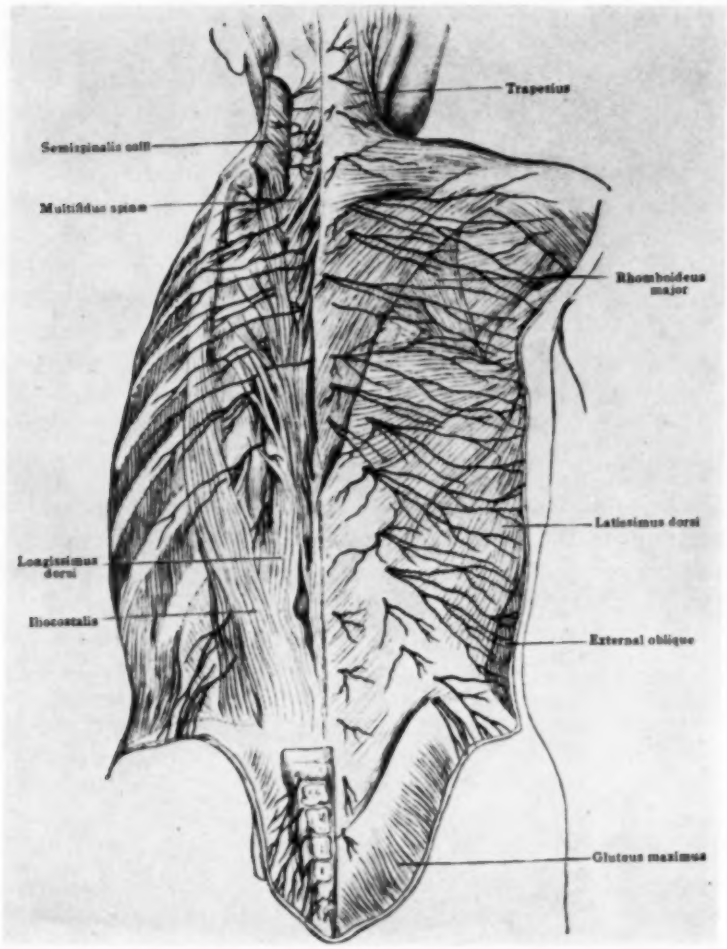

FIG. 2. Distribution of the posterior primary divisions of the spinal nerves (Henle).

possess protopathic sensations (Sherrington[18]), such an irritative process produces referral to the terminal portion of the nerve and, therefore, since these fibers run directly to the muscle bundles, muscular pain.

In this series of cases, however, as in Kellgren's observations, the widespread referred pain arises from the tender regions of the paravertebral muscles and interspinous ligaments. Since the somatic findings are always in close relation to arthritic spinal joints, it is reasonable to assume that the joint involvement is the primary cause and the muscular and ligamentous tenderness a secondary factor, either spasm or a localized "myositis" or "fibrositis." The widespread distribution of pain referred from the paraspinal muscles and its segmental relationship to the deeper visceral structures has been demonstrated by Kellgren. Simulated visceral pain occurs

because pain from the somatic structures is referred along the same path as that arising from a viscus (Lewis and Kellgren [19]).

The spinal nerves as they emerge from the intervertebral foramina divide into four branches: the anterior and posterior primary divisions, the small ramus communicans, and the smaller ramus meningeus. The posterior primary division after passing downward between the arches of the transverse processes divides (except the first cervical, fourth and fifth sacral, and coccygeal nerves) into medial and lateral branches, while the anterior primary divisions run laterally and ventrally as the direct continuations of the nerve trunks. As can be seen in figures 1 and 2, the paravertebral site of novocain infiltration includes the branches of the posterior ramus and more deeply the anterior ramus, as well as the muscles innervated by these nerves. A two-fold anesthetization is achieved in this manner so that, as a secondary effect, referral to the visceral structures is eliminated.

More difficult to explain, however, is the prolonged period of complete freedom from pain which follows the injection. Livingston [20] has ascribed the result of deep novocainization to the initial anesthetic action plus the expanding action of the solution itself. The fact that injection of normal saline is ineffective would seem to indicate that the novocain is a responsible factor. Gutstein-Good [21] and Moynahan [22] believe the pain of localized myalgias may be ascribed to the "vasomotor disequilibrium" theory of Leriche in which afferent impulses produced by local vasodilatation are responsible for the pain. The action of novocain is to block these impulses at their site of origin. Nevertheless, despite the absence of a satisfactory explanation of the underlying mechanism, empirically the method has proved extremely effective and, because of its simplicity and freedom from complications, merits continued clinical use.

Summary

1. The effects of novocain injection into the deep paravertebral muscles in patients with simulated visceral pain due to spinal arthritis are reported.

2. Two groups of patients with simulated visceral pain were encountered —those with and those without visceral disease. In both groups results were uniformly good.

3. Although the effect is probably due to the dissolution of a vicious reflex cycle, a complete explanation of the prolonged therapeutic result cannot be offered.

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CALCAREOUS PANCREATITIS; REPORT OF THREE CASES WITH AUTOPSIES *

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A CASUAL survey of the literature on diseases of the pancreas discloses surprising periodic surges of interest in this organ, some of which have been epochal. As our familiarity with pancreatic disorders increases, functional tests and diagnostic aids evolve and existing ones are used more critically.

Roentgenologic exploration of the abdomen is not yet on the same plane of precision and importance as the chest plate. Our knowledge and interpretation of anomalous shadows in the abdomen consequently have not attained the same diagnostic reliability. However, the increasing frequency of reports on pancreatolithiasis in the last few years is an indication of a growing familiarity with this condition. The roentgen-ray has taken pancreatolithiasis out of the category of rare lesions, in years past reported as an accidental finding at operation or necropsy. Although a roentgenologist's experience may not permit an unequivocal diagnosis of pancreatolithiasis in some cases, correlation of the abdominal shadow with the clinical disease, when symptoms are present, is usually diagnostic.

The following cases, in all of which an advanced calcareous pancreatitis was found at autopsy, presented several of the more important clinical features of the disease.

CASE REPORTS

Case 1. A white seaman, aged 57, entered the Marine Hospital July 1, 1941, because of severe weakness, intractable diarrhea and weight loss of 40 pounds within 10 months. The symptoms began insidiously about 18 months earlier. For the past 12 months, the patient had an average of 10 to 12 bowel movements daily. There was no associated pain or colic; the stools were watery, copious, and offensive in odor. They were described as containing "mucus and pus."

In August 1937, this patient was treated here for "rheumatism and an attack of colic." Roentgenograms made then showed minor hypertrophic changes in the knees and ankles. An impacted stone was found in the right ureter and further studies disclosed a right pyonephrosis. The Kolmer and Kahn tests were negative. The urine contained no sugar, and the blood picture was not significantly altered.

In September 1937, a right nephrectomy with ureteral lithotomy and ureterectomy was done. Convalescence was extremely slow.

Urinalysis January 3, 1938, revealed sugar 2+. The fasting blood sugar on January 5 was 375 mg. per cent. On January 7, the dextrose tolerance curve was of the severe diabetic type and all urine specimens showed 4+ sugar. After the diabetes was controlled, convalescence was rapid and uneventful.

Roentgenograms on April 3, 1938, showed absence of the right kidney, calcification to the right of the bodies of the third, fourth and fifth lumbar vertebrae and a calculus in the vicinity of the left ureter near the urinary bladder. From April 1938,

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until the onset of the present illness nearly two years later, the patient had been in fair health, worked hard, and made no effort to control his diabetes by diet or with insulin.

Physical examination at the present admission revealed pallor of the skin and mucous membranes, marked emaciation and muscular atrophy, and extreme dehydration. The tongue was beefy, red and furrowed. The patient was very weak and he had a hacking cough. The lungs were reported negative. The heart sounds were faint and there were numerous extrasystoles. Blood pressure was 75 mm. Hg systolic and 30 mm. diastolic. The abdomen was distended and tympanitic. There was no tenderness. The lower extremities showed marked pitting edema to just above the knees. Proctoscopic examination disclosed a minor degree of congestion of the rectal mucous membrane. The temperature was 37.6° C. on admission. The following day it was 39° C. and continued high until death.

The Kolmer and Kahn tests were negative. Urinalysis was negative. The red blood count was 4,000,000, hemoglobin 11 grams, and the leukocyte count and differential were within normal limits. The blood chemistry findings were: sugar 71, non-protein nitrogen 21 and chlorides 440 mg. per cent, respectively. The total protein was 5.7 grams/100 c.c. of serum and the A/G ratio was 1.03/1. Repeated stool examinations for parasites and cultures for pathogenic microörganisms were negative. A roentgenogram of the chest showed a dense shadow in the base of the right lung suggesting an infarct. Therapy of various types was of no avail and the patient died one week after admission.

Autopsy. The significant autopsy findings were as follows. The body was extremely emaciated and dehydrated. There was marked pitting edema of the scrotum and of the lower extremities from the mid-thighs down. The peritoneal surfaces were dry and lustreless. The urinary bladder was entirely empty. The loops of the small intestine were greatly distended with gas. The pericardial sac contained about 5 c.c. of normal fluid.

Lungs. The left lung weighed 1050 grams. The upper lobe was water-logged and the lower lobe showed extensive pneumonic consolidation. The right lung weighed 1900 grams. The medial side and base were inseparably fused with the paravertebral tissues. After removing the lung, a partially encapsulated abscess was found along the spine which apparently was part of the lesion in the lower lobe of the lung. On section, the parenchyma of the upper lobe showed extensive pneumonic consolidation. The lower lobe presented a large abscess marginated by smaller satellites. The bordering parenchyma was gangrenous.

Liver. The liver weighed 1700 grams. It was pale yellow in color and on section the parenchyma was of ordinary consistency. The gall-bladder was greatly distended with colorless watery fluid (white bile). The biliary ducts were patent and showed no lesions. The ampulla of Vater was prominent and the orifice contained granules of calcareous material, some of which were expelled after prolonged and vigorous pressure upon the gall-bladder.

Pancreas. Weight 400 grams. Its normal configuration was entirely lost. Handling imparted the impression of a sac filled with crunching and grating pebbles and stones. Satisfactory dissection of the organ could not be accomplished because it was entirely converted into a calcareous mass. Piece-meal dissection disclosed cystic spaces filled with multiple small and large hard, grayish, angular and sharp calculi. Deposits of hard gravel were present throughout the organ. Some of the cysts had a smooth wall and communicated with each other freely, apparently the remains of ducts. Pancreatic parenchyma was not demonstrable.

Aorta. The abdominal segment from the bifurcation upward presented a fusiform aneurysm 7 cm. in its greatest diameter and 10 cm. in length. The wall of the aneurysm was completely calcified. It was inseparably fused with and completely

compressed the inferior vena cava. The atherocalcareous process involved the common iliac arteries in their entirety so that they were pipestem in character.

Gastrointestinal Tract. The mucous membrane of the stomach was thin, ironed out and very pale. The wall of the intestines was thin and diaphanous. The mucous membrane throughout the intestinal tract showed advanced atrophy. There were no foci of ulceration or inflammation.

Histologic Examination. Histologic sections of the aortic aneurysm showed advanced diffuse atheromatous degeneration and calcification of the entire wall with little hyalinized scar remaining. The lungs showed confluent bronchopneumonia. The abscess in the left pulmonary base consisted of purulent necrotic material bordered by hemorrhagic and necrotic suppurating parenchyma. The liver showed extensive, advanced fatty metamorphosis of the hepatic cells.

The pancreatic parenchyma was practically entirely replaced by dense fibrous and hyalinized connective tissue. Rarely small groups of acini, showing more or less atrophy, were seen. Occasional islets of Langerhans remained. Some showed atrophic changes and others interstitial fibrosis. Cystic spaces of various sizes, having a dense fibrous wall, prevailed. In their wall isolated, atrophied and deformed acini were occasionally present. Segments of the wall were often incrusted with calcium. Here and there systems of dilated, distorted, ramifying ducts occurred. They had no lining or one of simple cylindrical or cubical epithelium. In the smaller ducts the epithelium showed short stretches of diffuse squamous metaplasia and hyperkeratosis. Some ducts were filled with desquamated cornified epithelium. In some it was mixed with amorphous calcified debris. Deposits of calcifying amorphous debris were present here and there throughout the fibrous stroma. In areas the fibrous tissue was vascularized and dense focal infiltrations of lymphocytes were present. The blood vessels of the pancreas showed diffuse fibrosis of their wall and the larger nerves showed more or less fibrosis of their sheath. Several large arteries showed more or less calcification of their wall.

Case 2. On September 17, 1941, a white male, aged 46, a sanitary inspector, was hospitalized for the treatment of pulmonary tuberculosis and diabetes mellitus. The patient had been under treatment for severe diabetes for two years. For the five months past, he had not followed his diet and used no insulin. During this period, he lost 40 pounds and became very weak. In April 1941, he had an attack of pleurisy. Roentgenograms disclosed a tuberculous lesion in the left lung. His health was growing progressively worse.

Physical examination revealed a pale, sick, febrile, coughing, emaciated patient. Laboratory studies disclosed a severe diabetes mellitus. Roentgenograms showed active tuberculous lesions in both lungs. The sputum contained acid-fast bacilli. Although the diabetes was completely controlled and the patient was on a rigid régime for his tuberculosis, the disease progressed rapidly and he died three and one-half months after admission. There were no abdominal symptoms at any time and he had had no diarrhea.

Autopsy. At autopsy both lungs showed chronic ulcerative tuberculous lesions in the apices and tuberculous bronchopneumonia throughout the remainder of the parenchyma.

Pancreas. Weight 180 grams. It was hard, granular and gritty. Sectioning disclosed the ducts to be dilated and filled with sharp, hard, angular, grayish-white calculi, some of which had cut their way into the parenchyma of the organ. In areas the main duct and its branches were cystic and filled with colorless fluid in which sandy material was present. Here and there throughout the organ chalky deposits and embedded collections of gravel were present. In areas remains of sclerosed parenchyma were detectable.

Histologic Examination. The histologic sections showed marked dilatation and

deformity of the ducts. Their wall was thickly fibrosed. Some were lined only by fibrous tissue and others showed focal calcification. The parenchyma was largely replaced by dense, acellular fibrous tissue. Here and their islands of acini ensnared in scar tissue remained. Very few islets of Langerhans were seen, some associated with acini and some solitary in the fibrous stroma. Deposits of amorphous calcified material were present apart from duct structures and these were often bordered by stray acini. In areas dense infiltrations of lymphocytes were encountered.

Case 3. A white male, aged 56, a known diabetic for more than 20 years, was hospitalized because of nervousness and mental confusion.

A history elicited from the patient's two sisters, both nurses, disclosed the following. The patient had had nausea, vomiting and severe diarrhea for the past five months. These attacks were occasionally associated with colic and pain over the stomach. The patient had no appetite and in a few months had become markedly emaciated. Despite repeated hospitalization and nearly constant medical attention the patient's abdominal condition was not diagnosed and treatment did not help. One year previously the patient had a periproctic abscess which was incised and drained, and healed. Now he had a painful lump in the same place.

Physical examination revealed a dull, apathetic, pale, emaciated patient. The oral mucous membrane was pale. There was moderate pitting edema of the lower extremities up to the mid-thighs; also the prepuce and lower eyelids were edematous. The temperature was 37.5° C. A large periproctic abscess which extended into the right ischiorectal fossa was present.

The urine contained a trace of albumin and no sugar. The blood chemistry showed sugar 128, non-protein nitrogen 29 and cholesterol 143 mg. per cent, respectively. The total protein was 4.2 grams/100 c.c. of serum.

Four days after admission the periproctic abscess was incised and drained. The abscess pointed to the right of the anus. It extended around the dorsal and ventral sides of the rectum and for some distance into the right ischiorectal space. Six days after operation another abscess appeared at the left side of the anus. It was opened and drained, and found to be an extension of the first lesion. Although the patient's diabetes was apparently under control, he lapsed into a state of stupor. Three days after the second operation the tissues around the anus and over the sacrum became black, fluctuant and crepitant. Cultures disclosed *Cl. welchii* and *B. coli*. The infection spread rapidly and the patient died two days after the onset of gangrene.

Autopsy. At autopsy the skin over the greater part of the back, the nates, around the anus, over the loins and over the posterior aspect of the left thigh was black, wet, gangrenous and emphysematous. Incisions into the gangrenous areas disclosed extensive hemorrhagic necrosis, copious extravasation of blood-tinged fluid and escape of gas bubbles from the fluid. Exploration of the periproctic tissue disclosed advanced suppuration and liquefaction of the perianal and perirectal tissues. Other significant findings were as follows.

Pancreas. Weight 250 grams. The specimen consisted of a deformed, sclerosed sac of stones. Piece-meal dissection disclosed several large sharp calculi in the head and numerous smaller ones throughout the duct system. Deposits of gravel were present throughout the sclerosed parenchyma. The ducts were dilated, cystic and sacculated. Whitish turbid fluid was present in some parts of the duct system.

Histologic Examination. Histologic examination disclosed a diffuse productive pancreatitis with practically complete replacement and destruction of the parenchyma. Large areas of liposis were present.

The lungs showed widespread tuberculous bronchopneumonia. The liver showed irregular fatty metamorphosis. The fundus of the gall-bladder was thickened. The bile ducts were moderately dilated, but showed no other changes. Subchronic dif-

fuse glomerulonephritis was present. There was advanced, generalized atherosclerosis. The abdominal aorta and common iliac arteries showed marked atheromatous ulceration and calcification of their wall.

Discussion

Etiology. The cause of stones in the ducts and calcareous changes in the parenchyma of the pancreas is not definitely known. In many cases the lesion has been associated with chronic disease of the biliary tract and with cholelithiasis. Infection by way of the ducts, regurgitation from the biliary tract, and stasis of pancreatic secretion are probably important contributing causes to the formation of duct stones. Squamous metaplasia of the duct epithelium is not infrequently observed. Desquamated, cornified epithelium may serve as a nidus for calcification in the ducts. Etiologic significance is also attributed to alcoholism in that some patients were chronic alcoholics. In a few cases cirrhosis of the liver, and fatty metamorphosis have been found. The fatty change in the liver is believed to be due to a disturbance in the secretion of a pancreatic hormone, lipocaic, which regulates the deposition of fat in the hepatic cells.

Calcification of the parenchyma is probably also a sequel of infection, inflammation and necrosis. Infection may occur by contiguity from adjacent structures, through the pancreatic ducts, or through the blood stream, but it probably occurs most frequently by way of the lymphatics. Free communication is present between the lymphatics of the pancreas and those of the biliary tract, stomach and duodenum.

A recent study [1] presents interesting observations that may explain the pathogenesis of chronic calcareous pancreatitis. In acute pancreatic necrosis, the fat necrosis has been shown to be due to the splitting of neutral fat into fatty acids and glycerin by the action of lipase that has escaped into the tissues from the pancreatic juice. The glycerin is absorbed and the fatty acids combine with calcium to form insoluble soaps. These authors demonstrated large quantities of calcium in acute pancreatic lesions, and they found a moderate fall in the serum calcium of patients with acute pancreatic necrosis, between the third and the eleventh day of the disease. Three instances of tetany associated with acute pancreatic necrosis have been reported.

In patients with pancreatolithiasis there is frequently a history of obscure attacks of abdominal pain and of episodes of vague gastrointestinal disturbances of variable severity, as in case 3 of the present series. These may well represent subclinical or abortive attacks of acute pancreatic necrosis. Once formed, a focus or foci of calcification continue to grow by the further addition of calcium salts. Secondary changes due to mechanical irritation and inflammation probably favor the progress and dissemination of the lesion to involve more or less of the pancreas. The mechanism of the influence of the parathyroids upon calcification is poorly understood, but an upset in the calcium balance may be a factor.

Calcification of the parenchyma may occur without associated concretions in the ducts, or gravel and calculi may be found only in the ducts. In advanced lesions the calcareous deposits occur throughout the pancreas and the most careful dissection and histologic studies cannot disclose which deposit was first.

The time required for stones in the ducts to form or for calcareous pancreatitis to develop is indefinite and highly variable. Pancreatic concretions are composed chiefly of calcium carbonate and calcium phosphate and, therefore, are likely to show in roentgenograms. In case 1 of the present series, roentgenograms of the abdomen made in 1937 and in 1938 showed no shadows in the region of the pancreas, yet two and one half years later ad-

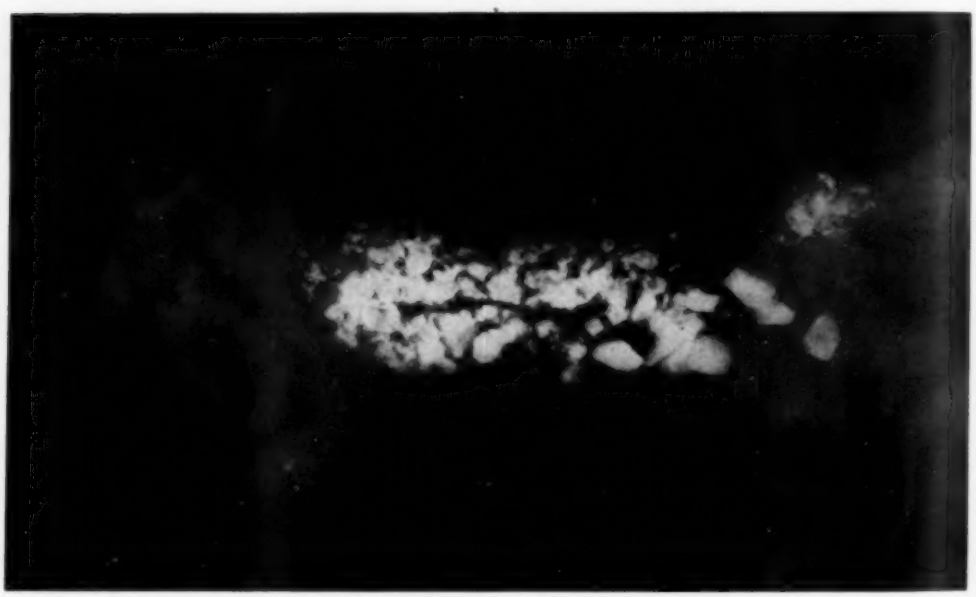

FIG. 1. Pancreas: roentgenogram of autopsy specimen showing extensive lithiasis (case 1).

vanced pancreatolithiasis (figure 1) was found at autopsy. Others have reported stone formation after shorter intervals and some after much longer periods of observation.

Pathologic Anatomy. The pathologic anatomy of calcareous pancreatitis affords the explanation for the pathologic consequences of the disease.

The concretions may consist of sandy or gravel deposits free in the ducts or incrusted over their wall. The ducts may be pipestem in character. Calculi as large as walnuts have been reported. Usually duct stones are multiple, or very numerous. They are of a grayish or brownish-gray color, hard, rough and angular, often sharp. They may be stag-horn or branched like coral. Sometimes they are facetted. The larger stones are usually found

in the head near the duodenal orifice of the pancreatic ducts, but they may be in any part of the gland. Gravel and stones may be deposited throughout the parenchyma of the pancreas. Usually parenchymal calcification consists of crumbly chalky gravel in large or small collections. Frequently the concretions are mixed with yellowish or chocolate colored organic matter.

The ducts are dilated, elongated and deformed. Not infrequently they show thickening and sclerosis of their wall and segmental cystic changes, and occasionally true retention cysts are formed.

The consequences of calculi and calcareous deposits are atrophy and progressive fibrosis with more or less destruction of the parenchyma of the

FIG. 2. Roentgenogram of calculus in Vater's papilla (case 1).

gland. The fibrosis is first interlobular and finally interstitial. The acinar tissue is affected first and most markedly. The islets of Langerhans are not significantly involved until the disease is far advanced. Only parts or all of the organ may be involved. Frequently it is converted into a sclerosed stony mass or into a sac of rocks. Suppuration and abscess formation may supervene in any stage of the disease. Stones may erode into the abdominal cavity or fragments may slip into the papilla of Vater as in case 1 of the present series (figure 2).

As a result of obstruction of the ducts or the destruction of the acinar tissue disturbances due to a deficiency of the pancreatic enzymes in the intestine may be conspicuous. Diabetes occurs when enough of the Langer-

FIG. 3. Roentgenogram of calcified aneurysm of aorta (case 1).

FIG. 4. Pancreas: roentgenogram of autopsy specimen showing extensive calcareous deposition (case 2).

hans islets are destroyed. However, even with advanced lesions there may be no symptoms, probably because the secretions of the stomach and intestines are capable of functioning vicariously.

Clinical Features. The clinical manifestations of calcareous pancreatitis are usually both vague and variable, and without roentgenograms a medical diagnosis of pancreatolithiasis could not be established. The more characteristic symptoms depend chiefly on the size, location and mobility of the stones in the main ducts and the secondary changes in or about the pancreas. Pancreatic colic is usually in no way distinguishable from biliary colic and was present in about two-thirds of the reported cases. The colic of pancreatic stone may be associated, however, with left sided extension and such pain may be further projected into the left costovertebral angle. The presence or absence of jaundice is not very significant, as jaundice is often lacking in cholelithiasis and is occasionally present in pancreatolithiasis. In the latter it may be due to compression of the common bile duct, or to obstruction of the papilla of Vater (figure 2).

It has been observed that episodes of acute pancreatic necrosis may occur with pancreatolithiasis. The symptoms are those of acute pancreatitis and should not be confused with pancreatic colic.

Various reflex digestive disturbances such as pylorospasm or gastrospasm, gastric hypersecretion, episodes of nausea and vomiting not associated with pain or colic, intestinal hypo- or hypermotility and other bizarre reactions which might be regarded as functional have been observed.[2]

Signs and symptoms of pancreatic insufficiency are present in about half of all cases of calcareous pancreatitis. Frequent bulky pale stools, marked inanition and extreme asthenia are the most characteristic clinical manifestations. Large amounts of fat and numerous undigested muscle fibers are present in the stool. Correlation of the signs and symptoms with visual examination of a 24 hour specimen of stool usually suffice for a presumptive clinical diagnosis, to be verified by roentgen examination, without which a diagnosis of pancreatolithiasis is practically impossible.

Physical examination may disclose tenderness in the epigastrium and an indefinable mass in the region of the pancreas, but usually it is not helpful.

It is significant that extensive damage to acinar tissue may be present without concomitant islet damage of sufficient severity to produce diabetes. However, latent and active diabetes mellitus is present in about 50 per cent of all cases of pancreatolithiasis. Often there is no evidence of associated pancreatic achylia. Obviously there is considerable variation in the amount of acinar and islet tissue destroyed, but also the magnitude of the disturbance in digestion and absorption that occurs when pancreatic insufficiency is present varies in different individuals. Diabetes may antedate the lithiasis by years, appear concomitantly, or develop after the lesion is far advanced. In case 1 of the present series diabetes was present at least two years before calcareous pancreatitis developed. Case 2 was a diabetic for two years

before he developed tuberculosis and died. Case 3 was a diabetic for more than 20 years before symptoms of pancreatic achylia ensued.

The statement that pancreatic duct stones are frequently found in diabetics has no support in the postmortem findings of large diabetic groups.[3] It is noteworthy that cholecystic disease and cholelithiasis occur in 25 to 30 per cent of diabetics and yet pancreatolithiasis is rarely found. These facts do not substantiate the statements that chronic biliary tract disease is an important etiologic factor and that pancreatolithiasis is frequently associated with cholelithiasis.

The clinical diagnosis of calcareous pancreatitis depends upon the roentgenographic demonstration of calcification in the pancreatic region. Pancreatic stones are usually sufficiently radiopaque to cast a shadow. However, it has been pointed out that they are best visualized in an oblique roentgenogram, and may often be missed in ordinary films of the kidneys, ureters and bladder or in cholecystograms. When the clinical disease is not suspected, shadows of stones in the pancreatic region may go unheeded or without proper interpretation.

Without special laboratory procedures, occasionally pancreatogenous diarrhea may be difficult to differentiate from sprue, idiopathic steatorrhea, celiac disease, exclusion of bile from the intestine, certain cases of enteritis and colitis, and other conditions characterized by frequent bulky stools. The diagnosis can be established by demonstrating (a) an absence or deficiency of pancreatic enzyme in duodenal drainage and (b) an excess of both fat and nitrogen in the stool. There is usually clinical improvement with oral pancreatic enzyme therapy.

Many of the reported cases of calcareous pancreatitis either had or died of pulmonary complications. In the present series, two patients died of tuberculous bronchopneumonia and one of pulmonary abscess and gangrene. It has been observed that patients with prolonged pancreatic insufficiency are predisposed to pulmonary tuberculosis, suppuration and gangrene. Obsolete or other tuberculous lesions have rarely been demonstrated in the pancreas.

Treatment. When the symptoms are principally those of pancreatic achylia oral pancreatic enzyme therapy is highly effective.[4] The response is characterized by a decrease in the frequency and bulk of the stools, associated with gains in weight and increased strength.

Cases not too far advanced are amenable to surgical treatment. A number of surgical successes have been reported.

Summary

Three cases of calcareous pancreatitis with autopsy findings are reported. The pathogenesis of the lesion, the pathologic physiology and the diagnostic features of the disease are presented.

Acknowledgment: I desire to express my appreciation to Drs. I. Apperman and R. A. Mee for the clinical data in cases 1 and 3, respectively.

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ALLERGIC REACTIONS TO LIVER EXTRACT*

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Reactions to liver extract, usually clearly of an allergic nature, have been reported by numerous authors [1-35] since 1931. These 35 articles record a total of only 50 patients experiencing reactions from liver extract by injection. The condition is by no means so rare, however, as the above number would indicate. In this article we are reporting 11 additional cases, four seen personally and seven whose detailed histories were given us by two of our colleagues (table 1). Dr. Guy Clark of the Lederle Laboratories wrote us that "over a period of several years we have received approximately 30 reports of rather serious allergic-like reactions following the parenteral administration of liver extract." [36] The medical director of another large laboratory has also told us of "several" such cases reported to him.[37] Some of the cases in the files of these companies have probably been published in various American journals, and may be included, therefore, in the total of 50 cases in the literature. Most internists and general practitioners have undoubtedly seen similar cases; and it seems certain that the physicians in every large hematology clinic have witnessed such reactions.

There have been a few reports [18, 38, 39, 40, 41, 42] of allergic reactions from the ingestion of liver, either raw or cooked, or of liver extract. The total number of cases described in these articles is only seven or eight. Thus, it seems that reactions are much less common when liver is taken orally than parenterally. This would appear logical when it is remembered that the reaction-producing substance in whole liver is markedly concentrated when an extract suitable for injection is prepared.

From an analysis of the cases of reactions from injections of liver extract,[1-37, authors] it appears that the make of extract has little or no relation to the incidence of such reactions. Reactions have occurred after injections of all of the following: the original, moderately crude extract used by Murphy in Boston; the most concentrated commercial product, Reticulogen; various other Lilly extracts; several Lederle varieties; Parke, Davis' extract; Cheplin's extract; and the European preparations: Campolon, Exhepar, Eparina, Examen, Pernaemon, Hepatrat, and Heptomin. Many patients experiencing reactions from one brand also had reactions from other makes. The amount of extract injected may be the determining factor in some instances, but not in all. One patient [32] had a reaction after the administration of but 0.2 c.c. Campolon, a relatively dilute extract. Some patients have experienced generalized allergic manifestations after as little as 0.1 c.c. in-

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tracutaneously,[7, 9, 10] and one had a severe local reaction after a test dose with the minute amount of 0.1 c.c. of a 1 : 1,000 dilution intracutaneously.[16] One of our patients (case 2) usually had a reaction after 1.0 c.c. Reticulogen, whereas 0.5 c.c. was usually tolerated.

A remarkable and inexplicable fact is that most patients have their first reaction after numerous injections and then never have another, even though receiving the same brand and the same quantity. This may be due, in some

TABLE I

Allergic Reactions to Liver Extract Injections

	Patient 1	Patient 2	Patient 3	Patient 4
Age	57	48	55	52
Sex	M	F	F	M
Other allergic manifestations	None	None	None	None
Make and amount of extract given	Lederle's ext. 3 c.c.; Reticulogen 1 c.c.	Lederle's ext. 3 c.c.; Reticulogen 0.5 c.c.–1.0 c.c.	Lederle's ext. 3 c.c.; Reticulogen 2 c.c.	Lilly's conc. ext. 3 c.c.
No. of injection when reaction occurred	Reaction many times; after many injections	Reaction many times; after many inj.	Reaction once; after many inj.	Reaction after 1, 2, 5 inj.
Clinical manifestations	Congestion and itching of conjunctivae and sclerae; edema, redness, itching of hands; occasional tightness in chest with cough. (Similar type reaction with both makes ext.)	Epigastric and sub-xiphoid pain with nausea and occ. vomiting—similar to pt's spontaneous anginal attacks. (Similar type reaction with both makes extract.)	Pounding and pain in head; flushed face; watering of eyes; taste of liver ext. (Reaction once only: after an injection of Lederle's ext. 3 c.c.)	First: urticaria; Second: scarlatiniform eruption; Third reaction: erythema, itching, and edema of arm.
Time from injection to onset of reaction	10–20 minutes	3–10 hours	Less than 1 minute	1.10 minutes 2.5 minutes 3.12 hours
Time reaction lasted	15–45 minutes	½–4 hours	5 minutes	1. 36 hours 2. Few hours 3. 4 days
Treatment given	Adrenalin with relief	Nitroglycerine with relief	None	Ephedrine; calamine lotion
Subsequent injections	Yes	Yes	Yes	Not after third reaction
If so, what reactions	Gradually desensitized: w. Reticulogen	Gradually desensitized: w. Reticulogen	None	—
Skin tests with liver extract	Yes (see chart)	Yes (see chart)	Yes (see chart)	No

TABLE I—(*Continued*)

	Patient 5	Patient 6	Patient 7	Patient 8
Age	54	68	37	32
Sex	F	F	F	M
Other allergic manifestations	None	None	?	None
Make and amount of extract given	Lederle's ext. ? c.c.; Reticulogen: ? c.c.; Cheplin's ext. 5 c.c.	Cheplin's conc. ext. 2 c.c.	Reticulogen 0.5 c.c.	Reticulogen 0.5 c.c.
No. of injection when reaction occurred	Lederle's: ? inj.; Reticulogen: after 7 inj.; Cheplin after 50 inj.	After 7th. inj.	After 1st. inj.	After 2nd. inj.
Clinical manifestations	Angioneurotic edema of lips and eyelids; general urticaria. (Similar type reaction after all 3 makes of extract.)	Urticaria of arms and wrists	Urticaria of face and arms	Pruritic, erythematous, maculopapular eruption—generalized.
Time from injection to onset of reaction	15 minutes	30 minutes	1 hour	2 days
Time reaction lasted	2 hours	30 minutes	Few minutes	12 days
Treatment given	Ephedrine	None	None	?
Subsequent injections	Yes	Yes	No	No
If so, what reactions	None	None	—	—
Skin tests with liver extract	No	No	No	No

instances, to inadvertent intravenous injection. Very rarely a reaction occurs after the first injection (case 4, this paper), but much more commonly the initial reaction is noted after the product had been well tolerated for weeks, months, or even years,[18, 30, 36, 43, authors] and especially after a long interval since the previous injection. This is apparently characteristic of allergic reactions from biologic products. As Criep[43] has well expressed the situation: "There is no prediction when an allergic reaction to a biological product may develop or when it will fail to develop. A patient may show a reaction to an injection today, none for the next two or three injections, and then another reaction later. These patients do not react with the same unfailing constancy following exposure to the respective allergens

TABLE I—(*Continued*)

	Patient 9	Patient 10	Patient 11
Age	68	40	71
Sex	F	F	F
Other allergic manifestations	None	None	None
Make and amount of extract given	Reticulogen 1 c.c.	Reticulogen 1 c.c.	Reticulogen 1 c.c.
No. of injection when reaction occurred	After 10th inj.	After 8th inj.	After 20th inj.
Clinical manifestations	Swelling and itching of palms	Itching of entire body	Itching of entire body
Time from injection to onset of reaction	1 hour	30 minutes	1 hour
Time reaction lasted	2 hours	3 hours	6 hours
Treatment given	Local	Local	None
Subsequent injections	Yes	No	No
If so, what reactions	None	—	—
Skin tests with liver extract	No	No	No

that atopic persons, such as hay fever patients, show when exposed to pollen." Sensitivity to liver extract may persist for long periods of time, even up to eight years in one instance.[27]

The average age of the 41 patients exhibiting reactions, whose ages were stated in the published reports, was 50 years. The youngest, with one exception—a 10-month-old infant [14] who was omitted from the average—was 24; the oldest was 73. Of the 47 patients whose sex was recorded, 33 or 70 per cent were females. Of the 61 cases of reactions to liver extract (including our 11) reported in the literature, only six are definitely stated to be allergic patients; 13 are definitely stated to show no other allergic manifestations, and in the remainder no statement is made.

Clinical. The clinical manifestations of reactions from liver extract are very varied. The commonest is urticaria, either alone or in association with other allergic symptoms. Local reactions, with pain, edema, erythema, and itching, are probably more common than the number of such cases in the literature would indicate, since frequently such relatively slight reactions, compared with the more dramatic occurrences, have probably not been considered important enough to warrant publication. Angioneurotic edema has been reported in many patients, as has asthma. A typical, severe, generalized reaction was reported by Grün.[10] His patient, a 56-year-old female with primary anemia, had been receiving injections of Exhepar without incident for some time. A few minutes after an intramuscular injection

weakness, a rapid and weak pulse, vomiting, dyspnea, urticaria, and a marked fall in blood pressure were noted; recovery occurred after administration of adrenalin. Diena [7] reported the case of a 73-year-old female who developed abdominal pain, nausea, vomiting, urticaria, sweating, tachycardia, and dyspnea a few minutes after the third injection of Campolon. Another patient, a 39-year-old male, noted warmth and flushing of the face and neck after the fifteenth liver extract injection; generalized urticaria, followed the next day by generalized glandular enlargement, appeared after the sixteenth injection; and perspiration, asthma, tachycardia, and urinary incontinence followed the seventeenth injection.[4] Hafström's patient [17] developed severe anaphylactic shock with edema and urticaria, collapse, loss of sphincter control, and cyanosis. Segerdahl's patient [22] had flushing of the face, injection of the conjunctivae, pain in the back, oppression in the chest, and asthma. Roovers [25] reported one patient who had severe asthma with pulmonary edema, and a second who had pain locally, edema of the face and tongue, and tingling in the fingers. Kuipers [24] described a patient who showed angioneurotic edema, an exanthem, generalized itching, and pain in the joints. An interesting reaction was reported by Chaudhuri [6]: shortly after the first injection of 2 c.c. Campolon into the right gluteus muscle, there appeared itching, pain and swelling over the left deltoid muscle, followed by generalized itching and urticaria. Held and Goldbloom [5] report a remarkable combination: on several occasions their patient developed renal colic, urticaria, erythema nodosum, pruritus, and pain in the right knee joint after the intramuscular injection of liver extract. Engel [16] had a patient who experienced a tremendous local reaction with edema and redness, nausea, diarrhea, and weakness after a test dose of 0.1 c.c. intracutaneously. Gardner [39] described the unusual occurrence of weakness, dizziness, palpitation, and uterine bleeding on several occasions after various oral preparations of liver extract. If we mention the case [17] with severe nasal and ocular discharges and substernal oppression, almost the whole gamut of allergic manifestations will have been described. No fatalities have been reported.

Tests. Intracutaneous testing with various brands of liver extract has been reported by many investigators.[2, 7, 8, 9, 10, 11, 13, 14, 16, 20, 29, 33, 34, authors] The total number of patients who had allergic reactions from liver extract and who were subsequently tested intracutaneously is 26, of whom 24 showed positive skin tests. The passive transfer technic was employed additionally by several authors.[2, 7, 9, 10, 11, 14, 16, 20, 29] Of 11 patients thus studied, eight showed positive tests. Several investigators used 0.1 c.c. of the extract, which is too large an amount for most intracutaneous tests, as it will frequently give false positive reactions. We feel that one should employ 0.02–0.03 c.c. with a maximum of 0.05 c.c. The interpretation of the results of the intracutaneous tests with liver extract is difficult. Allin and Meyer,[44] using 0.05 c.c. undiluted liver extract, found that 14 of 15 normal individuals developed wheals, and therefore "arbitrarily decided that the appearance of wheals per se was not considered representative of a positive reaction, but

that any reaction showing pseudopods should be taken as positive." We found, from a study of some normal individuals, that with the diluted extracts in amounts even as small as 0.02 c.c., a wheal up to 12 to 15 mm. in diameter is normal. Therefore, the reaction was not considered positive unless the wheal was over 15 mm. in diameter or unless pseudopods were present; and the latter were never noted unless the wheal was over 15 mm. in diameter. As examples of our interpretation, a wheal 12 by 15 mm. with no pseudopods is negative; a wheal 16 by 20 mm. with no pseudopods is one plus; a wheal 22 by 25 mm. or 20 by 30 mm. with or without pseudopods is two or three plus; and a wheal 22 by 40 mm. with pseudopods is four plus.

TABLE II

Skin tests

Allergen	Scratch	Puncture	Intradermal undiluted 0.02 c.c.	Intradermal diluted 1 : 10 0.02 c.c.	Intradermal diluted 1 : 100 0.05 c.c.
Patient 1					
Reticulogen	+	+	++++	++	+
Lederle's ext.	neg.	neg.	+++	+	neg.
Lilly's ext.	neg.	neg.	+	+	neg.
Pork muscle	neg.	neg.	neg.	N.D.	N.D.
Beef muscle	neg.	neg.	neg.	N.D.	N.D.
House dust	neg.	neg.	neg.	N.D.	N.D.
Ragweed	neg.	neg.	N.D.	N.D.	N.D.
Patient 2					
Reticulogen	neg.	neg.	+	+	+
Lederle's ext.	neg.	neg.	neg.	neg.	N.D.
Lilly's ext.	neg.	neg.	neg.	neg.	N.D.
Pork muscle	neg.	neg.	neg.	N.D.	N.D.
Beef muscle	neg.	neg.	neg.	N.D.	N.D.
House dust	neg.	neg.	neg.	N.D.	N.D.
Ragweed	neg.	neg.	N.D.	N.D.	N.D.
Patient 3					
Reticulogen	neg.	+	+++	neg.	N.D.
Lederle's ext.	neg.	neg.	neg.	neg.	N.D.
Lilly's ext.	neg.	neg.	+	neg.	N.D.
Pork muscle	neg.	neg.	neg.	N.D.	N.D.
Beef muscle	neg.	neg.	neg.	N.D.	N.D.
House dust	neg.	neg.	neg.	N.D.	N.D.
Ragweed	neg.	neg.	N.D.	N.D.	N.D.

N. D.—not done.

Positive intradermal reactions to liver extract have been reported [29] with dilutions up to 1 : 100,000. Positive skin tests have persisted as long as one year after the occurrence of the allergic reaction.[10] Immediate [7, 10, 16] and delayed [9] generalized reactions from intracutaneous testing have occasionally been extremely severe. One of these immediate reactions, after the intradermal use of 0.1 c.c. undiluted extract, consisted of a tremendous local

edema and redness, in addition to nausea, diarrhea, and weakness.[16] Harten and Walzer [18] have pointed out that "the danger of employing 0.1 c.c. for intracutaneous testing in such cases is obvious."

Precipitins and anaphylactic antibodies have been searched for in a few instances.[11, 29, 34, authors] In Criep's one case [29] precipitins to liver extract were present in serum dilutions up to 1 : 100, but anaphylactic antibodies were not demonstrable. Gigante [11] was also unable to demonstrate them in either of his two cases. Taylor and Hilger [34] found precipitins in the serum of both their patients. We were unable to get a single positive precipitin reaction to three different makes of liver extract even with undiluted serum from the three patients whose blood we investigated (table 1, cases 1, 2, 3).

Cause. The cause of reactions to liver extract injections is not entirely clear, and it is likely that there is more than one type of reaction. We agree with Harten and Walzer [18] that "there is little doubt that some of the cases which have been reported as allergic reactions to liver extract really belong in the group of histamine-like reactions." Heinsen,[45, 46] in Germany, and Clark,[36] of the Lederle Laboratories in this country, have found histamine or a histamine-like substance in many batches of liver extract used commercially. Choline-like substances have also been demonstrated.[36, 47] Certain cases described in the literature [1, 24, 48, 49, 50] and possibly case 3 in this paper appear to be of this type.

The large majority of the reactions following liver extract injection or ingestion are undoubtedly true allergic reactions. This opinion is based mainly on the clinical picture, with the positive intradermal tests and the presence of reagins and precipitins as corroborative evidence. A question of considerable theoretical interest is whether the sensitivity is to liver as an organ or to the biological source; i.e., to the animal from which the liver was obtained. Sixteen patients showing allergic reactions to liver extract were carefully studied with this problem in mind.[2, 20, 29, 33, 34, authors] All had positive intracutaneous reactions to various brands of liver extract, and many had positive passive transfer reactions additionally. These patients were all tested with the muscle protein extracts, and in some cases with the serum, of the animals (swine and beef) from which liver extracts are prepared commercially. In every instance, with one exception—a patient incidentally allergic to beef—negative reactions were obtained, indicating that the sensitivity is to liver as an organ and not to the animal species. Feinberg, Alt, and Young,[33] who studied eight of these patients, go even further and state: "The [allergic] specificity appears to be due to a special organ [liver] fraction not found with the ordinary protein but associated with the anti-anemic fraction." In the present state of our knowledge concerning the chemistry of the anti-anemic fraction, that would appear to be merely an assumption, although we can be reasonably certain that the sensitivity is to some substance in liver, irrespective of its biological source. Hypersensitiveness to the liver allergen cannot be produced at will, even in allergic patients, as Criep has demonstrated.[29]

Treatment. The symptomatic treatment of allergic reactions to liver extract is simple: adrenalin or ephedrine and calcium preparations for the generalized type, and in addition local applications, such as calamine lotion with phenol, for urticaria or pruritus. The avoidance of reactions presents a more difficult problem. Perhaps Tausk [51] is correct in saying that it may be "possible to avoid these reactions when the anti-anemic substance has been isolated in pure state." However, up to the present, even with marked concentration of the anti-anemic factor in certain liver extracts, the reactions have not been eliminated nor do they seem to be less frequent. It is our impression, from a review of the literature and from observation of our own cases, that without the therapeutic measures to be discussed, patients allergic to liver extract can tolerate the intramuscular injection of only approximately a certain number of units of anti-anemic substance, irrespective of whether it is administered in dilute or in concentrated form. Thus certain patients who usually have a reaction from 0.2 c.c. of an extract containing 20 units per c.c.—a total of 4 units—will probably have a similar reaction from 4 c.c. of an extract containing 1 unit per c.c.—again a total of 4 units. This is by no means an invariable rule; and as pointed out earlier, with the majority of patients allergic to liver, it is impossible to predict when an allergic reaction will develop. However, those few patients (such as our case 2) who usually do react to a certain number of units of anti-anemic substance and who usually do not react to a lesser number, irrespective of the concentration, tend to substantiate the contention that "the specificity appears to be due to a special organ [liver] fraction not found with the ordinary protein but associated with the anti-anemic fraction." [33]

The simplest method of avoiding reactions is the discontinuance of liver extract, which may be done when the patient does not have primary anemia. Changing to oral preparations may help to avoid reactions, but it is generally agreed that the oral treatment of primary anemia is not so effective as the intramuscular. Taylor and Hilger [34] recommend the use of histaminase. The intradermal tests with liver extracts were "definitely less pronounced" in their two patients while they were taking histaminase. However, they did not show that the clinical reactions were thus reduced, and one would not like to have to administer that preparation during all the years of liver extract therapy in cases of primary anemia. A more useful and feasible therapeutic agent for those patients who react frequently might be histamine in gradually increasing subcutaneous doses. This procedure has been shown [52, 53, 54] to produce a histamine refractoriness and to ameliorate or eliminate many allergic conditions.

Finally, there is the question of desensitization with gradually increasing doses of diluted liver extract. Many authors [1, 4, 7, 10, 13, 14, 20, 32] have claimed good results with this method; and we feel, from a study of those reports and especially from close observation of two of our patients (cases 1 and 2), that this is an excellent method for those patients who react regu-

larly or frequently. Naturally there have been occasional failures,[16, 27] as with any therapeutic procedure in clinical medicine. In the technic of desensitization there has been much variation. Engel[16] started with a 1 : 1,000,000 dilution, and Pache[20] with a 1 : 100,000,000 dilution. On the other hand, Andrews[32] started with minute amounts of undiluted extract; but from his description of the case, it appears to us that he would probably have achieved better progress had he used diluted extract at the beginning, although the final result was excellent. We began desensitization in our two cases with 0.1 c.c. of a 1 : 10 dilution and increased by about 0.2 c.c. every second or third day for about three weeks until the patients were receiving the average full therapeutic dose (Lederle's extract 3 c.c. or Reticulogen 0.5–1.0 c.c.). We believe it important to keep this type of patient "desensitized" by giving the therapeutic injections in smaller quantities and at more frequent intervals than is customary; i.e., at least once a week.

Of course, it is necessary to attempt desensitization only in those patients who react regularly or frequently. For those who have one reaction and never another, such as our case 3, no such measure is needed. One should always have adrenalin, a sterile syringe and needle, and a tourniquet at hand when giving liver extract or any other biological product by injection. Although we favor an attempt at desensitization in certain patients, it is only fair to point out that "the results obtained by this method should be subject to guarded interpretation,"[18] since "spontaneous loss of sensitivity may explain the reports of successful, complete desensitization which occasionally appear in the literature."[40]

Summary and Conclusions

1. A review of the literature of allergic reactions to liver extract has been presented, and 11 additional cases have been reported.

2. The make of extract and the dose have little relation to the occurrence of such reactions.

3. Reactions usually occur after numerous well-tolerated injections, especially after a long injection-free interval.

4. The clinical manifestations are extremely varied, including practically every allergic sign and symptom.

5. Direct and indirect intracutaneous tests with various brands of diluted extract are usually positive, whereas similar tests with hog and beef muscle are usually negative.

6. Although a small number of the reported reactions are probably due to preformed histamine, the large majority are on a true allergic basis.

7. The sensitivity is to some substance—possibly the anti-anemic factor—in liver extract, irrespective of its biological source (hog, beef, etc.).

8. Desensitization with gradually increasing doses of diluted liver extract is recommended for patients who react frequently.

Addendum. Since this article was accepted for publication, another paper has appeared which gives a good review of this topic (FEINBERG, S. M., ALT, H. L. and YOUNG, R. H.: Allergy to injectable liver extracts: clinical and immunological observations, ANN. INT. MED., 1943, xviii, 311). Also two additional cases of unusual allergic reactions to liver extract have been brought to our attention. One was an allergic patient who was tested intradermally with liver extract and within a few minutes developed a severe anaphylactic shock, almost fatal. The other was a patient who became comatose and subsequently developed a hemiplegia shortly after an injection of liver extract. The opinion of several clinicians was that the injection was the direct cause of a cerebro-vascular accident of an allergic nature.

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THE MANAGEMENT OF PAROXYSMAL TACHYCARDIA INCLUDING THE USE OF MECHOLYL*

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PAROXYSMAL supraventricular tachycardia is a common functional heart disorder of all ages but particularly of young adults without organic heart disease. Relatively few attacks are seen by physicians, since attacks cease spontaneously or the patient has learned ways of stopping them. Of the persons seeking medical aid for this arrhythmia, a few find their attacks resist ordinary physical means and oral therapy and persist for hours and sometimes many days before they spontaneously cease. Deaths have been recorded,[3] as have hemiplegia and gangrene [9] as thrombotic sequelae of the low pulse pressure and minute output during such attacks. A history of paroxysmal tachycardia rejects applicants for army air crew and flying personnel and electrocardiographic evidence is cause for rejection of army officer candidates,[1] but since first attacks are common in young adults it is probable that Army Surgeons will occasionally have to manage such problems.

Advice for the prevention of attacks is principally directed to extracardiac somatic factors and these vary with the individual patient. If drugs are indicated because attacks are frequent and tend to persist and annoy the patient, quinidine is best, but an occasional patient responds better to digitalis. Sedatives are helpful in the physician's program of reassurance, and sometimes are all that is required when observant patients realize that a contemplated experience may precipitate an attack. A typical example was that of a young college instructor who told me several years ago that he was subject to attacks when he traveled to see his sweetheart whom his family disliked as much as her family disliked him, but that the attacks could be prevented by 15 grains of bromides.

It is recognized that the psychic factor is a great one in these problems from several angles. It may act as a direct precipitating factor for attacks and a healthy person may develop an incapacitating neurosis because of ill founded notions of the significance and prognosis of his disorder. Reassurance, therefore, must be definite and backed by proved ability to terminate attacks as promised. The published facts are that people have been known to have attacks for over 50 years and have no influence on longevity, and if organic heart disease exists the prognosis depends on the underlying heart disease.[4]

A healthy vigorous man of 73 told me that he had had attacks occasionally for 30 years and had learned long since to disregard them. His son, 50, was just becoming convinced after five years' similar experience that his

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attacks were no cause for concern. He knows carotid sinus pressure stops them and that 1½ grains of digitalis every second day will prevent them and that quinidine is less effective. Some form of carotid sinus reflex elicitation will stop the majority of attacks. The patient deserves to be carefully instructed in carotid sinus pressure, ocular pressure, the Mueller and Val Salva experiments and told about the benefits of postural change and vomiting. These six physical procedures in addition to some schemes which his experience may have taught him provide an armamentarium which in itself offers more than passive reassurance. Pressure on the eyeballs has to be enough to cause the patient some discomfort and the patient should look down while pressure is exerted. The Mueller and Val Salva experiments are easy for the patient to execute without notice, since in one the patient strains to exhale but keeps his glottis closed and in the other he strains to inhale but keeps his glottis closed. Various combinations of these procedures have caused slowing of paroxysmal fast heart rates when single procedures have failed. To induce vomiting, apomorphine has been used and syrup of ipecac in doses of from one to four drachms [9, 19] has been a favorite of some good clinicians as a treatment of attacks.

When the physical methods have been tried or before trying them the patient can be instructed to take his usual dose or a double dose of quinidine at two hour intervals for two or three doses or until tinnitus is noticed. In this manner patients have tolerated as much as 100 grains in one day.[19] If there is any tendency for him to develop an apprehensiveness, he should be provided with an effective sedative which he can take early in the attack and allow himself to assume a semirecumbent or recumbent position unless he knows that such positions tend to bring on attacks.[5] It has been thought that not until such procedures have been well tried and heart tones are becoming less vigorous or signs of basal râles or very annoying systemic signs have appeared was one justified in using parenteral quinidine or mecholyl or intravenous strophanthin or digitalis. One reported attack of 10 days' standing, several years ago, was stopped when quinidine had failed with 15 cat units of digitalis intravenously.[22] Just recently intravenous metrazol has been used with satisfactory results.[2] Intravenous quinidine is frequently referred to in the literature but I have encountered no reliable available preparation for this purpose. Just recently Sturnick, Riseman and Sagall [16] pointed out that "soluble preparations of quinidine sulphate for parenteral administration have not been readily available." This statement is true despite the fact that solutions of quinine dihydrochloride are commercially available in ampoules and have been administered intramuscularly and intravenously and dilute solutions of quinidine sulphate in dextrose or water and suspension of quinidine sulphate tablets in hot water and hydrochloric acid have been used in emergencies.[21] Sturnick, Riseman and Sagall [16] published their experiences with a preparation recommended by the Cinchona Products Institute, but the preparation requires more than average facilities since sterilization was achieved by passage through a Berkefeld filter. If the

preparation could be made commercially available it would apparently be an improvement over quinidine preparations now in use. The drip method of intravenous quinidine administration is the safest but it takes such a long time that one can wonder whether it was quinidine or the passage of time which stopped the tachycardia.[12] In the choice of any heroic procedure it is comforting to know that the effects of the drug can be quickly stopped at any moment and in that regard mecholyl has an advantage over the others.

For terminating attacks mecholyl, now council accepted for this purpose, is advised in the War Department's Technical Manual entitled "Notes on Cardiology in Aviation Medicine," and it has received increasingly favorable mention in the literature since first described for this purpose by Starr in 1933.[18] Detailed comment on the drug's history, its action and a practical scheme for its use have been omitted from most articles concerning the treatment of paroxysmal tachycardia.

The use of the various cholines has been a development of the present age. Acetylcholine was first synthesized by Baeyer in 1867 but had only a chemical interest. In 1914 Dale noted that the chemical mimicked the effects of stimulation of the parasympathetic nerves. Starr and others later made investigations which have provided a sound basis for the use of available cholines in medicine.[6] Acetyl-beta-methylcholine or mecholyl is one of the few cholines stable enough and with sufficient investigation behind it to deserve a place in our therapeutic armamentarium. When it reaches the tissues it is probably in a form which duplicates products of the body itself. Its greatest usefulness is in treating paroxysmal supraventricular tachycardia, and it has no place in treating other arrhythmias. It has been used in persons of all ages from infancy to old age. Atropine or epinephrine will abolish its effects and quinidine tends to block its action. Oral administration has been unsatisfactory either to prevent or stop attacks.[6, 13] Mecholyl should never be given intravenously, since the effects of hypodermically administered therapeutic doses are so rapid and dramatic that anyone who has not been appraised of them should familiarize himself well with the effects, and should not undertake to use the drug unless he follows very carefully a set procedure. However, if this is done, the physician can avail himself of an effective agent which he can control at will.[12, 13]

I have had only a few patients whose attacks have failed to respond as desired to oral quinidine, sedatives and the physical measures mentioned, but I decided to use mecholyl on resistant electrocardiographically proved supreventricular tachycardias after a visit to Dr. Starr's Clinic several years ago. Though I have employed it in treating only 12 attacks, the effect has been so uniform and in accord with the descriptions of the investigators that I feel the drug merits wider use. Even among competent internists I have encountered a sense of fear and hesitation when use of this drug is mentioned. Starr has always advised that in giving mecholyl "one should have a syringe of atropine ready for intravenous administration" but lately adds that he has not had to use it for many years, since he simply applies a tourniquet above

the site of injection when the action appears excessive as shown by nausea and vomiting. Since the effect of mecholyl on the bronchial tree is to cause bronchial spasm, it has been suggested that in asthmatic subjects the drug be either not used or else even greater care than usual be employed. In hyperthyroid patients mecholyl is capable of inducing auricular fibrillation and for this reason hyperthyroidism is sometimes considered a contraindication for this therapy though Starr has noticed no ill effects from mecholyl in such cases.[6, 12]

The patient receiving mecholyl should be recumbent, since the erect posture at the height of the drug's action may cause fainting. A bed pan should be ready for the same reason in case the subject should have a sudden desire to defecate during the drug's action [6] which is a possibility though none of my patients has had more than active audible peristalsis.

It is well to explain to the patient and to any relatives who insist on being present during the treatment each of the subjective and objective manifestations of the mecholyl effect before giving the injection. In less than a minute a brilliant flush comes in a wave over the blush areas, perspiration and salivation are profuse, and peristalsis becomes audible. Even if appraised before, the patient usually makes some comment concerning these things because they come so quickly. A medical colleague whose tachycardia I terminated with mecholyl without a previous sedative was so impressed that he decided to refer any resistant tachycardias for such therapy, and he volunteered the suggestion that the use of such a drug should be in the hands of someone other than a general practitioner such as himself. Having used the drug both with and without the previous administration of a sedative, I believe it is better to administer something to dim slightly the perceptive senses before using mecholyl. For this I have used a therapeutic dose of morphine sulphate. I have recently discussed this with Dr. Starr who says it is perfectly proper and who, although he has not used a sedative, is interested in the idea.[12] So with the patient and nurse or relative posted on coming events and contraindications considered and a sedative in effect, one can proceed.

The average dose of mecholyl for adults is 20 to 50 milligrams and it is available in sealed glass ampoules of the dry drug each containing 25 milligrams. The contents of each ampoule are easily soluble in 1 c.c. or less of sterile distilled water introduced into the ampoule. So that no confusion arises one can either use differently marked syringes or place the empty mecholyl ampoule over the needle of the syringe filled from it. Atropine gr. $\frac{1}{50}$ in solution ready for intravenous injection is in the second syringe. The arm with easily accessible veins is selected and a blood pressure cuff is applied or good tourniquet placed loosely high on the upper arm. Mecholyl is then administered subcutaneously below or distal to the blood pressure cuff which is not inflated. At the moment the heart rhythm and rate return to normal as detected by the stethoscope over the precordium, the blood pressure cuff is inflated to prevent further absorption and to make a vein ready if desired for

the administration of atropine. The return to sinus rhythm has occurred in my experience as early as 80 seconds following the mecholyl injection and has been reported in less time. If no effect on rate is noted by the time the drug is at its peak effect as manifested by flush in the blush areas, perspiration, salivation and loud peristalsis (2 to 10 minutes) Starr has suggested massage of the site of injection and also carotid sinus stimulation by one of the above physical means.[13] This is necessary in some 20 per cent of cases. If no effect is manifest 30 minutes after the injection, another dose can be given. The drug does not lose its effectiveness by repeated use as indicated by a report of its successful use in stopping 15 of 16 attacks recurring in a child over a two year period.[23] I have had a similar successful experience in eight attacks out of nine in a middle-aged woman over a three year period.

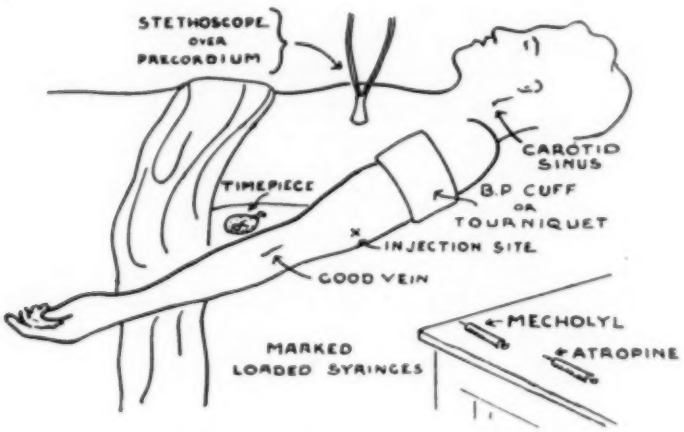

FIG. 1. Mecholyl administration; patient recumbent.

The first time it was used on this patient it was ineffective because only 25 milligrams were given and no second dose was used and later experience demonstrated that 40 to 45 milligrams were needed. On several occasions she had 8 to 10 grains of quinidine within three hours of satisfactory mecholyl treatment, which supports the statement that mecholyl can break through the quinidine effect. The reliability and short time necessary to abolish the tachycardia which this woman has been having occasionally for 25 years have made her grateful. Most of her attacks cease spontaneously or with repeated oral doses of quinidine, but if they persist for a few hours she now has them stopped whereas previously she has been incapacitated at least a day or two. In a middle-aged man whose attack had resisted usual therapy for 10 hours a second dose of 60 milligrams reinforced with carotid pressure was given with success after one of 40 plus carotid sinus stimulation plus massage of the site of injection had failed.

No deaths have been reported from the use of the drug, but reports are available of great overdose (10 and more times the therapeutic dose) and mistaken intravenous administration and in each instance recovery was complete.

Each of my patients' rhythm was proved electrocardiographically but I was not fortunate enough to secure a tracing during the transition to normal sinus rhythm. Such tracings have been published[13] and support what one hears with the stethoscope. In each attack that I have treated with mecholyl the rapid rhythm was interrupted by a brief period of asystole, then the next few beats seemed slightly slower than the normal sinus rhythm which was quickly established. The quick transition from a heart rate of 160 to 180 to one of 70 or 80 with the brief asystole is usually noted by the patients, though the relief from the rapid rate is ample reward for the brief moment of what they have termed a "funny feeling."

Summary

1. Paroxysmal supraventricular tachycardia is a common functional cardiac abnormality usually seen in normal hearts but has been fatal and has led to disabling thrombotic conditions. A history of it disqualifies for air crew and flying personnel, and electrocardiographic evidence is cause for rejection in candidates for army commissions, but since the first attack may occur at any age it is probable that cases will be observed occasionally in our armed forces. Most attacks do not require medical attention, but it is estimated that 10 to 20 per cent defy the patient's efforts to stop them.

2. To prevent attacks direct therapy is usually not indicated, but attention is given extracardiac somatic factors; reassurance to the patient and investigation of psychic factors are indicated; if drugs are desired quinidine sulphate is most effective, digitalis is occasionally more satisfactory, and sedatives usually help.

3. Therapy of attacks: Carotid sinus reflex elicitation; sedatives; oral quinidine. If the latter is ineffective, digitalis has been used either orally or parenterally, but mecholyl is perferred if parenteral therapy is indicated.

4. Advantages and steps in the use and control of mecholyl are outlined and cases cited.

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TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS: CURRENT RESULTS*

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SULFONAMIDE chemotherapy has proved disappointing in subacute bacterial endocarditis. Final judgment of its merit must be reserved, however, until the incidence of recovery in a large series of treated cases is compared with spontaneous recovery in the pre-sulfonamide era.

In a preliminary survey of 288 cases of subacute bacterial endocarditis treated by current methods, Lichtman and Bierman [1] deduced that chemotherapy and supplementary measures produced recovery in a small but significant percentage of cases. This survey has been continued with the aim of obtaining correct answers to the questions:

1. Is sulfonamide chemotherapy responsible for recovery in subacute bacterial endocarditis?
2. Do supplementary therapeutic measures, i.e., heparin, artificial hyperpyrexia, etc., enhance the results of chemotherapy?

MATERIAL

The cases previously reported [1] are here supplemented by reports in the literature, unpublished communications, and cases treated at The Mount Sinai Hospital up to April, 1942. The series now includes 98 cases of subacute bacterial endocarditis due to *Streptococcus viridans, Hemophilus influenzae* and enterococcus from The Mount Sinai Hospital and 606 cases collected from other sources, a grand total of 704 cases. Cases due to the gonococcus were not included; only adequately treated groups of cases were selected.† Seven recovered among the Mount Sinai cases,‡ and a total of 39 in the entire study. The material is presented under the headings:

Spontaneous recoveries reported in the literature.
Recovery with the use of sulfonamide drugs.
Recovery with the use of "combined methods," i.e., sulfonamide combined with heparin or fever therapy.
The results with other forms of treatment.

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† This is arbitrarily fixed at a *minimum* of two weeks of intensive sulfonamide medication; seven artificial hyperthermia treatments, six intravenous injections of typhoid vaccine, and heparinization for two weeks with a blood coagulation time of one hour, respectively.

‡ Two private cases treated by Drs. E. P. Boas and Elmer Gais, respectively, recovered and are included with their kind permission. Cases are regarded as recoveries when they are afebrile and repeated blood cultures are negative for a *minimum* period of three months after the use of sulfonamides has been discontinued.

Spontaneous Recoveries: These are recorded in table 1. Libman's experience leads with four recoveries among 150 cases carefully studied and followed,[2] and subsequently 12 among 1,000,[2] and 22 among 1,500 cases.[3] Single recoveries have been reported by Horder in 150, by Kissling in 43, by Middleton and Burke in 88 cases, and also by Weber,[8] respectively. There were no spontaneous recoveries among 815 cases reported by other observers (table 1). The incidence of spontaneous recovery among 2,596 collected cases was 1 per cent.

TABLE I

Spontaneous Recoveries in Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries
Libman [2]	1,500	22
Horder	150	1
Thayer	206	0
Warren and Herrick	25	0
Morrison [4]	145	0
Fulton and Levine [5]	111	0
Kissling	43	1
Schulten et al.[6]	200	0
Major	15	0
Middleton and Burke [1]	88	1
Middleton and McCue [7]	23	0
Steele	30	0
Herrell and Brown [9]	60	0
Total	2,596	25
Per cent Spontaneous Recovery	1.0	

Recovery with Sulfonamide Drugs: The results of sulfonamide chemotherapy are presented in table 2. Recoveries among *groups* of cases have

TABLE II

Results of Sulfonamide Chemotherapy in Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries
Major	7	3 (Viridans)
Kinell and Ernstene	5	0
Spink and Crago	11	1
Klee and Romer	4	0
Ellis	2	0
Whitby	3	0
Bliss, Long and Feinstone	3	0
Kolmer	10	0
Steele	10	0
Long [7]	187	8 (Viridans)
Leach, Faulkner, Duncan & McGinn [10]	18	1 (Viridans)
Porter and White [10]	11	0
Middleton and McCue [7]	5	0
Herrell and Brown [9]	80	0
Field, Hoobler and Avery [11]	31	1 (Viridans)
Kinsella [12]	19	0
Heyer and Hick [13]	14	1
Bickel and Mozer [14]	8	2
Smith, Sauls, and Stone [20]	15	1
Mount Sinai	46	3 (2 Viridans; 1 *Hemophilus influenzae*
Total	489	21
Per cent Recovery	4.0	

been reported by Major,[1] Spink and Crago,[1] Long,[7] Leach et al.,[10] Field et al.,[11] Heyer and Hick,[13] Bickel and Mozer,[14] Smith, Sauls and Stone,[20] and in the Mount Sinai series. Twenty-one recoveries were reported in a combined series of 337 cases and no recoveries in another combined series of 152 cases. The incidence of recovery with the use of sulfonamides alone in a total of 489 cases was 4 per cent.

Isolated successfully treated cases have been reported by McQuarrie,[1] Barton and Stinger,[1] Lian and Frumusan,[15] Heyman,[1] Christie,[1] Christie and Parker,[16] Druckman,[17] Jersild,[18] and Andrews.[19] Smith, Sauls and Stone [20] collected 35 reports of cures.

Recovery with Combined Methods of Treatment: A. *Chemotherapy and Heparin:* A total of 109 cases with seven recoveries belong in this group (table 3). Recoveries in heparinized patients are listed by Kelson and White,[1] Leach et al.,[10] Kelson,[10] McLean et al.,[21] and one by us. The incidence of recovery in the entire heparinized group was 6.5 per cent. B. *Chemotherapy and Artificial Hyperthermia:* Sixty-one cases received artificial fever therapy. Levine and Gibson [22] observed one definite recovery among 12 cases and another case is now apparently cured for three months. Three patients observed by Bierman and Baehr [23] among 34 cases treated at The

TABLE III

Results with Combined Methods of Treatment of Subacute Bacterial Endocarditis

	Number of Cases	Number of Recoveries	Percentage of Recoveries
Chemotherapy, heparin			
Kelson and White [1]	7	2	
Leach, Faulkner, Duncan, McGinn	16	1	
Kelson [10]	20*	3**	
Field, Hoobler, Avery [11]	5	0	
McLean, Meyer, Griffith [21]	28***	1	
Herrell and Brown [9]	26	0	
Mount Sinai	13	1 (Viridans)	
	109	7	6.5
Chemotherapy, hyperthermia			
Krusen and Bennett	11	0	
Porter and White [10]	4	0	
Levine and Gibson [22]	12	1 (Viridans)	
Mount Sinai	34	3 (2 Viridans; 1 Hemophilus)	
	61	4	6.5
Chemotherapy, intravenous typhoid			
Solomon [24]	22	5 (Viridans)	
Porter and White [10]	3	0	
Middleton and McCue [7]	7	0	
Davidson and Shlevin [25]	8	2 (Viridans)	
Mount Sinai	5	0	
Total	45	7	15.5

Six * cases and one ** recovery of Mount Sinai Series included.
*** After deduction of cases already included in this table.

Mount Sinai Hospital recovered and now follow normal lives.* Two were cases of *S. viridans* and one of *Hemophilus influenzae* endocarditis. The incidence of recovery in 61 cases was 6.5 per cent (table 3).

Forty-five cases received combined sulfonamide chemotherapy and *intravenous typhoid vaccine.* Clinical recoveries from this method of treatment have been observed by Solomon [24] and Davidson and Shlevin.[25] The incidence of recovery among 45 cases was 15.5 per cent (table 3).

Miscellaneous Forms of Therapy: Middleton and Burke [1, 7] employed radiotherapy in 12 cases and it was combined with sulfonamides in six cases at The Mount Sinai Hospital without success. Radiotherapy was employed in cases with recovery reported by Bierman and Baehr [23] and Smith, Sauls and Stone,[20] but its effective value discounted in both instances.

TABLE IV

Summary of Results of Treatment of Subacute Bacterial Endocarditis

Method of Treatment	Number Treated	Number Recovered	Percentage Recovered
Sulfonamide Chemotherapy *			
Mount Sinai	46	3 (2 Viridans; 1 Hemophilus)	
Literature	443	18	
	489	21	4.0
Combined Therapy **			
Mount Sinai	52	4 (3 Viridans; 1 Hemophilus)	
Literature	163	14	
	215	18	8.5
Total Cases			
Mount Sinai	98	7	7%
Literature	606	32	5%
Total	704	39	5.5%

* Sulfonamide compounds (sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine).
** Chemotherapy combined with (1) heparin, (2) radiotherapy, (3) hyperthermia, (4) intravenous typhoid-paratyphoid vaccine.

Neoarsphenamine has been employed in over 70 cases. Osgood [26] analyzed the protocols of 34 cases treated with this arsenical and listed four recoveries. There were also 36 other cases without detailed protocols, six of whom remained symptom-free for several months. The evaluation of the status of neoarsphenamine therapy awaits the results of further trial. Isolated failures have been noted by Middleton and McCue [7] and in the Mount Sinai series.[1] Lippmann [27] reported a case of recovery after combined sulfonamide and solarson (1 per cent ammonium heptenchlorarsonate) therapy.

* Treated under the supervision of Dr. William Bierman, Physical Therapist to Mount Sinai Hospital.

Dicoumarin, possessing heparin-like properties, has as yet been applied in too few cases to estimate its value as a substitute for heparin.

Surgical ligation of the ductus arteriosus in cases of subacute bacterial endocarditis superimposed on patent ductus arteriosus affords the best prospect of recovery of all the methods of treatment. Surgical procedure, however, is applicable only to the small number of cases of subacute bacterial endocarditis developing on the basis of this congenital anomaly. Recovery in well over 50 per cent of cases with patent ductus and subacute bacterial endocarditis is reported by Touroff et al.,[28] and by Gross.[29]

Comment

The phenomenal results of sulfonamide chemotherapy in the treatment of infections emphasize its relative failure in the treatment of subacute bacterial endocarditis. Even the occasional recovery from this disease following chemotherapy is viewed with skepticism, an attitude which is unwarranted since recoveries undoubtedly occur. To disclaim the authenticity of all recovered cases casts doubt also on the occurrence of spontaneous recoveries. In each recovery it is justifiable to deliberate whether the *Streptococcus viridans* is a secondary invader in a case of active rheumatic carditis,[30] or the microörganism in a septicemia without bacterial endocarditis.[31]

It is more consistent to accept recoveries in patients with the established clinical criteria of subacute bacterial endocarditis as authentic than to question the accuracy of diagnosis or the therapeutic result, on the general principle that recovery in this disease occurs rarely if ever. The recent increase in reported recoveries is probably due to early recognition and effective sulfonamide treatment of mild cases. Undue skepticism of results in this type of case thwarts the prospect of better results by early diagnosis and treatment. Recoveries may be few and far between, but an increased rate of recovery, no matter how small, represents a significant advance in treatment. A 3 per cent rise in recovery rate above the incidence of spontaneous recovery of 1 per cent means the survival of an additional 30 individuals in 1,000 cases. This is not phenomenal, but it represents a substantial triumph for the 30 survivors who are usually fit to return to normal life.

The incidence of spontaneous recovery may be accepted as approximately 1 per cent (table 1). Four per cent of patients with subacute bacterial endocarditis treated by sulfonamide chemotherapy appear to recover. The rate of recovery in patients treated both by a combination of sulfonamides and heparin and by sulfonamide and artificial hyperthermia was 6.5 per cent. The significance of the increase from 4 to 6.5 per cent of recovery may be questioned. Decision as to the value of heparin must be withheld until the results of treatment are compared with those in a series of cases in which bacteremia and fever have been reduced to nil by sulfonamide medication alone. Comparison will demonstrate whether heparinization influences recurrence of bacteremia once effectively sterilized by sulfonamide chemotherapy. Until this comparison is made the contention will constantly be

raised that the alleged favorable results of heparinization are due merely to selection of sulfonamide-cures for this form of treatment. The future of the use of heparin in this disease is further conditioned by many claims of an increased incidence of fatal cerebral hemorrhage and also by the fact that bacteremia is controlled at least temporarily by available sulfonamides in only approximately 10 per cent of patients with the disease. Since persistent bacteremia precludes the use of heparin, this form of therapy is restricted in its application.

The increase from 4.0 to 6.5 per cent recovery in sulfonamide-treated patients, supplemented by artificial fever therapy on the other hand, probably represents a truer increase in effectiveness of sulfonamide chemotherapy since hyperthermia produced results *after* failure of sulfonamide and other forms of treatment.[1]

Favorable response to artificial hyperthermia in *Hemophilus influenzae* endocarditis should not be discounted on the basis that this organism is especially thermosensitive. Bierman and Baehr [23] noted recovery in a case of subacute *Hemophilus* endocarditis treated by combined sulfonamide and fever therapy but a parallel case treated in the same manner at the same time failed to respond. The prognosis of endocarditis due to this organism is not materially different from *Streptococcus viridans* endocarditis.[32]

The unusually high incidence of recovery following the use of intravenous typhoid vaccine and sulfonamides is remarkable but it is doubtful that this degree of success will mark the results in a large series of cases so treated.

The results of surgical ligation of the ductus arteriosus in subacute bacterial endocarditis superimposed on the patent ductus are phenomenal. Surgical management of this form of endocarditis is accompanied by prompt surgical success in well over 50 per cent of cases. The choice between surgical and medical management of these cases is influenced by the following factors: immediate surgical death occurs in a small percentage of cases; sulfonamide cures are reported in a small but definite number of cases; fever persists and death from endocarditis ensues in some cases despite the ligation of the ductus and resulting negative blood cultures. In rare instances subacute bacterial endocarditis develops after prophylactic ligation of a patent ductus.[34] Occasionally the diagnosis of patent ductus or associated congenital lesions is erroneous or the vegetative process extends beyond the ductus arteriosus up to the aortic valve and aorta. In conservative hands, surgical ligation should be attempted promptly after failure of medical measures.

Summary

The results of current methods of treatment of subacute bacterial endocarditis are disappointing; however, a small but significant number of patients recover. The recovery rate among a total of 704 cases was found to average 5.5 per cent. Of 489 cases treated by sulfonamide chemotherapy, 21 recovered, an incidence of *4 per cent;* among the remaining 215 patients treated by chemotherapy, supplemented by heparin or fever therapy, 18

recovered or 8.5 per cent. Of 109 heparinized patients, seven recovered, an incidence of *6.5 per cent*. Of 61 patients treated with artificial fever therapy, four recovered, an incidence of *6.5 per cent* recovery. The incidence of spontaneous recovery in subacute bacterial endocarditis is estimated at approximately 1 per cent.

Supplementary measures may increase the recovery rate in subacute bacterial endocarditis treated with sulfonamides. Artificial fever therapy supplementing sulfonamide chemotherapy produced a slight but significant increase in recovery rate from 4 to 6.5 per cent and intravenous typhoid vaccine appeared also to produce an increased recovery rate subject to further trial. The evaluation of heparinization as a supplementary measure of treatment requires further trial in properly controlled material. Surgical ligation performed on patients with patent ductus arteriosus complicated by subacute bacterial endocarditis produced the highest percentage of recoveries. Unfortunately, however, this cardiac anomaly occurs in only a minor number of cases of subacute bacterial endocarditis. An estimation of the therapeutic value of neoarsphenamine and dicoumarin awaits further trial.

Spontaneous recovery is acknowledged to occur in approximately 1 per cent of cases. Failure to encounter recovery in a large series of cases of subacute bacterial endocarditis treated by current methods does not justify the arbitrary blanket rejection of all published reports of recovery as spurious cases of subacute bacterial endocarditis. The factors responsible for individual recoveries cannot be formulated. Until methods of treatment and results are improved further, every patient with subacute bacterial endocarditis should receive intensive sulfonamide chemotherapy to tolerance. The choice of supplementary therapeutic measures rests at present with individual preference.

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PSYCHOSIS DUE TO SULFONAMIDES*

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Various toxic reactions to the sulfonamides have been described, and among the more uncommon manifestations of toxicity is psychosis. There are numerous cases of psychosis reported following the administration of sulfanilamide.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12] Long,[2] although listing the incidence of psychosis during the use of sulfapyridine at 0.3 per cent, states that no sulfathiazole psychosis has yet been reported. Brown, Thornton and Wilson[3] report delirium in seven patients of a series of 100 cases given sulfapyridine. Two cases received less than 25 grams and five received over 25 grams in less than 10 days. Wyrens[4] states that mental disturbances are uncommon following either sulfapyridine or sulfathiazole administration but does not quote any figures. During the past 13 months there have occurred in the Station Hospital at Camp Blanding, Florida, two episodes of psychosis during the administration of sulfonamides which I wish to report, as they occurred in patients under sulfathiazole and sulfadiazine therapy.

Case Reports

Case 1. S. K., Private, white, male, aged 28, was admitted to the Station Hospital, Camp Blanding, Florida, April 8, 1941, weighing 145 pounds and complaining of having been ill one day with fever, sore throat, productive cough, chill, and generalized aching. His past history was non-contributory. On examination, the patient showed evidence of an upper respiratory infection with a temperature of 101.2° F., pulse rate 96, respiratory rate 20. The laboratory studies showed: urine normal, white blood cell count 12,900, hemoglobin 70 per cent, and red blood cell count 3.3 million. On the night of April 10 his cough became worse, and he complained of a pain in his chest. Physical examination showed evidence of consolidation of the left lower lobe, and sulfathiazole therapy was begun, the patient receiving two grams at the first dose and one gram every four hours thereafter. A roentgenogram on the following day confirmed the diagnosis of left lower lobe pneumonia, and the patient continued to receive one gram of sulfathiazole every four hours, the temperature returning to normal on April 11. The next day, on the afternoon of April 12, about 48 hours after the first dose of sulfathiazole, the patient became talkative, nervous and irrational. The drug was withdrawn, but 12 hours later the psychosis had advanced so far that the patient was delusional and hallucinated in the auditory and visual fields, requiring treatment in a closed psychiatric ward. On April 15, 72 hours after onset, he regained orientation, lost his hallucinations and delusions but remained somewhat apprehensive. By April 16 he had regained his normal mental state. In all, the patient received 13 grams of sulfathiazole over a period of 48 hours. At no time during the illness did the patient appear extremely intoxicated and his sensorium was clear during the febrile period, the delirium coming on after a 12 hour period of normal temperature. On recovery there was no memory of the psychotic episode. Unfortunately, in this case the type of the organism and blood sulfathiazole levels were not determined.

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Case 2. B. O., colored, male, CCC, aged 17, weighing 125 pounds, was admitted on April 11, 1942, because of cough, chill, pain in his chest, fever and bloody sputum of 12 hours' duration. His past history was non-contributory. Physical examination showed a rather undernourished colored man in a moderate degree of toxemia, who appeared acutely ill. The heart was normal except for rapid rate and accentuated second pulmonic sound. Examination of the lungs revealed signs of consolidation in the right lower lobe, later confirmed by roentgenogram. The sputum showed pneumococci, type VII, with over 11 per high power field. The white blood cell count was 42,500, the hemoglobin 85 per cent, red blood cell count 5.0 million, and urinary findings normal. The temperature was 104° F., pulse rate 110, respiratory rate 36, blood pressure 105 mm. Hg systolic, and 66 mm. diastolic. Sulfadiazine was started at 4:00 p.m., April 11, 1942, the initial dose being four grams and one gram being given every four hours thereafter. His temperature returned to normal the following day, the patient feeling well and mentally clear. On the morning of the third day, approximately 40 hours after the first dose of the drug was given and after 24 hours of normal temperature, he awoke complaining that his father and brother had been shot and that he must go home at once. His reaction to this delusion was so great that he attempted to get out of the window. The drug was discontinued while the temperature was still normal, sulfadiazine blood level being 6.8 milligrams per 100 c.c. At this time the patient was oriented as to time, place and person, but a few hours later he became disoriented and had visual and auditory hallucinations. He heard the voices of his relatives and saw brightly colored objects such as green trucks, green snakes, green spiders and pink hats. Twenty-four hours after withdrawal of the drug, the blood level reached two milligrams per 100 c.c., and there was a recurrence of his pneumonia with temperature reaching 104° F. About four hours later, 28 hours after cessation of the drug, he became mentally clear with the temperature still 104° F. The patient received 14 grams of sulfadiazine in 40 hours, and his highest blood level was 6.8 milligrams per 100 c.c. After the recurrence of the pneumonia and clearing of psychosis, he was treated successfully with small doses of sulfathiazole instead of sulfadiazine. It may be noted here that as long as the sulfathiazole blood level was kept below 4.0 milligrams per 100 c.c., the patient was mentally clear, but when sulfathiazole blood level reached 5.2 milligrams per 100 c.c., the patient became delusional in the same manner as he did when under sulfadiazine administration. At the onset of this delirium, the patient was given large quantities of intravenous fluids and his delusions cleared within four hours, the blood sulfathiazole level receding to 4.0 milligrams per 100 c.c. within an hour after recovery. This delusional state occurred after the administration of 14 grams of sulfathiazole and approximately 60 hours after the initial dose. After recovery there was no memory of the psychotic episodes.

Discussion

A search of the literature reveals a great number of cases of toxic psychosis precipitated by sulfanilamide but few from other sulfonamides. In the cases reported by Brown, Thornton and Wilson [3] occurring with sulfapyridine, delirium was most frequent in those who received over 25 grams in less than 10 days. In the two cases reported in this paper, the psychosis occurred within 48 hours of the first dose of the drug: in the case of sulfathiazole, after the administration of 14 grams; with the sulfadiazine, after 13 grams. I am not considering the recurrence of delusions in case 2 following the administration of sulfathiazole as an additional case report, but I would

like to bring out the fact that this delusional state occurred 60 hours after the first dose of sulfathiazole and after the administration of 14 grams of the drug.

It may be argued that in case 2 the psychosis was caused by the fever and other toxic effects of the pneumonia, but I do not believe that is the case as the psychosis occurred after the patient had been afebrile for 24 hours and cleared while the temperature was 104° F. with a recurrence of the pneumonia.

The psychosis in each case was quite similar, and both were actively delusional and hallucinated in auditory and visual fields. The psychosis in the first case lasted longer and was more violent.

Summary

Two cases of psychosis following administration of sulfonamides are reported. Both cases occurred during the first 48 hours of treatment and after approximately the same amount of drug (sulfathiazole, 14 grams and sulfadiazine, 13 grams). The psychosis with sulfadiazine lasted 28 hours and with sulfathiazole 96 hours. Although there are too few cases reported to draw any accurate conclusions, one is led to believe that psychosis from the administration of sulfapyridine, sulfathiazole and sulfadiazine occur early. Both of the psychoses cleared without ill effects, although case 1 required treatment on a closed psychiatric ward and case 2 required constant attention.

Conclusion

1. Psychosis may occur following the administration of sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine.

2. When mental aberrations are noted, they are likely to be cumulative and must be carefully observed, as the patient is likely to become frankly psychotic.

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CASE REPORTS

THROMBOCYTOPENIC PURPURA COMPLICATING ACUTE CATARRHAL JAUNDICE; REPORT OF A CASE, REVIEW OF THE LITERATURE, AND REVIEW OF 48 CASES OF PURPURA AT UNIVERSITY HOSPITAL*

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THE purpose of this paper is (1) to report a case of thrombocytopenic purpura complicating acute catarrhal jaundice; (2) to present a review of all of the cases of purpura at the University Hospital with reference to jaundice; and (3) to report a review of the literature on this clinical picture.

CASE REPORT

The patient, a 14 year old white boy, was admitted July 27, 1939 from the Rosewood State Training School. Little is known of the past history other than that he was illegitimate, and both parents were deceased. His early years were spent in a county home, the latter at the above mentioned training institution. Past illnesses included several attacks of tonsillitis, and jaundice with fever in 1938. The latter attack was short in duration and was not associated with purpura.

The present illness began seven days prior to admission with headache, anorexia, and general malaise. The patient stated that he did have a little fever and that his stools were light in color, with dark colored urine. (A report from the institution revealed that he had bile pigments and bile salts in the urine.) No medication was used other than a saline purgative and a proprietary capsule consisting of bile salts. Icterus was noticed on the third day of the illness, accompanied by intense itching. On the following day the patient noticed small, red, non-elevated areas on the chest and abdomen which soon became generalized, covering the entire body. Stools at this time were dark in color and on two occasions black. Bleeding from the gums began two days prior to, and continued up to admission. There was slight nausea at this time but no vomiting, and other than the bleeding and itching the patient felt quite well. No history could be obtained of eating mushrooms, taking toxic drugs, tick bites, or other possible causes.

Physical Examination: The patient was a well developed white boy, alert and oriented, and deeply jaundiced. The body was completely covered with myriads of hemorrhagic, non-elevated areas varying in size from a pinhead to a quarter. None faded on pressure. The mucous membrane of gums, soft palate, and pharynx was also studded with purpuric spots. The sclerae were deeply icteric, with minute hemorrhages present. The fundi were normal with the exception of two small petechiae on the right side. Nose: There were petechiae on the mucous membrane. Mouth: There was free bleeding from the lips and gum margin. The mucous membrane was studded everywhere with petechiae. The tonsils were quite large and chronically infected. There were a few large glands in both anterior cervical groups which were not tender. Heart and lungs were essentially negative. The liver extended three fingers' breadth below the costal margin and to the fourth rib anteriorly. The edge was sharp but not tender. The tip of the spleen was easily palpated.

* Received for publication March 8, 1940.

TABLE I

Summary of Laboratory Examinations of Case Reported

Date	Platelets	Ict. Index	Van. d. Bergh	Bleeding T.	Clotting T.	Prothrom. T.	Liver F.			Bl. Fibrinogen	Blood Chem.				Urine		Stool		Bile	Tourniquet T.	Bl. Culture	Fragility T.	R.B.C.	W.B.C.
							Galact. Tol.	Hippuric Ac.	Bromsulf. T.		Bl. Amino Acid	N.P.N.	Bl. Sugar	Bl. Ca. and P	Bile	Urobilin	Benzid.	Guaiac						
July 27	39,070	106	9.3	12¼′	13′	12″						27	96	9.4	++	++	++++	++++	+	6		0	4.4	5,100
28														4.4	+	+								
29	38,200						5.4										++++	+++	Tr.	97	0		4.5	
30	39,310						gm.																4.6	
31	55,930																						4.3	
Aug. 1	57,070	172	19							.27					+	0	++	0	+				4.4	
2	85,080									gm. %					+	0	+	0	0				4.1	
3	115,360			5¼′	11½′	12′									+	+	++	Tr.	+	4			4.1	
4		116	10					1.04			6.6	23			Tr.	0	++	Tr.	+					
5	106,310							gm.			mg. %				Tr.	0							4.1	
6															0	0	0	0						
7	197,760	80	6															0					4.1	
8															0	0								
9	385,400	64	4.3												0	0		0					4.1	
10																								
11																								
12		43	3														0	0						
13																								
14																								
15		48	3	2¼′	2′										0	0								
16	569,800																						3.7	
17																								
18																								
19															0	0								
20																								
21		25	2.3																					
22																								
23	688,500																						4.3	8,300
24																								Retic.
25		23	1.9																					4.4%
26															0	0								
27																								
28									0															
29																								
30																								
31																								
Sept. 1							1.6																	
2							gm.																	

Extremities: The legs and arms were completely covered with petechiae varying in size. There was no cyanosis nor clubbing of the nails. Platelet count was 39,070. The urine contained bile pigments and bile salts with urobilin. No cystine or leucine crystals were noted. Tourniquet test revealed six additional petechiae. Stool showed occult blood and trace of bile.

Clinical Course: There was slight fever, the maximum temperature observed being 99.8° F. The tonsils were injected, and on the fourth day one of the right cervical lymph nodes became enlarged and tender. Under treatment which included administration of placental extract, calcium lactate in large doses, cevitamic acid and two transfusions, each of 100 c.c. of citrated blood, the bleeding ceased after three days. The platelet count rose more slowly. Jaundice continued to be intense until the seventh day after admission, with clay colored stools, then it gradually faded. The liver and spleen diminished in size. The patient was discharged September 2, 1939, apparently well except for a faint tract of jaundice.

Laboratory Examinations: Data of significance are summarized in table 1. There was evidence of impaired liver function, as shown by the high icterus index, strongly positive direct van den Bergh reaction, high excretion of galactose and low excretion of hippuric acid. There was, however, no increase in prothrombin time and fibrinogen was normal.

Biliary drainage on the sixth day yielded only a small quantity of "A" bile, which showed *E. coli* in culture. A guinea pig inoculated with urine on the ninth day did not show *Leptospira icterohemorrhagiae*.

TABLE II

Summary of 48 Cases of Purpura from the Records of the University Hospital

Diagnosis	Number of Cases	Platelets Below 60,000	Jaundice	Died	Splenectomy	Splenomeg.
Thrombocytopenic purpura	26	9	0	4	3	8
Acute yellow atrophy	1		1	1	0	0
Symptomatic purpura	11	0	2	3	0	0
Arthritic purpura	10	0	0	0	0	0

Cases of Purpura at the University Hospital. A total of 48 cases of purpura of all types was found in the records of the University Hospital. Of these, 26 cases, or 54 per cent, were placed in the idiopathic thrombocytopenic group. The remainder were equally distributed between the arthritic and symptomatic forms, the former group including the cases of purpura simplex and anaphylactoid purpura of the Schönlein-Henoch type. These are summarized in table 2.

None of the cases of thrombocytopenic purpura showed any clinical evidence of jaundice. One, however, had a delayed direct van den Bergh reaction with 2.4 mg. per cent of bilirubin in the serum. In this particular case the spleen was palpated and complete recovery followed splenectomy. The platelets rose postoperatively from 59,000 to 470,000 in three days. No evidence of liver damage was noted. Included in this group are three cases of purpura believed due to a deficiency of vitamin C, which were treated effectively with large doses of cevitamic acid. In one case the spleen was irradiated following which there was a slow rise in the platelet count from 160,000 to 260,000 in five days. Three cases developed as a complication of pregnancy, all of which made a favorable

recovery. In none of these did the platelet count become lower than 180,000. Three cases in the hemorrhagic group came to splenectomy, following which there was a prompt rise of platelets and recovery. Hepatic function tests were not done because there was no clinical evidence of liver damage.

The one case of acute yellow atrophy is considered because of the purpura which developed terminally. In this patient there was widespread liver destruction, evidenced by an icteric index of 257, a direct prompt van den Bergh reaction with 20.3 mg. per cent of bilirubin, and a blood amino acid of 16 mg. per cent. Urinary bile pigments were 4 plus. Unfortunately, blood platelets, bleeding and clotting times were not recorded. Necropsy revealed a widespread central necrosis with a few scattered petechial hemorrhages.

One case in the symptomatic group is significant in that the purpura developed during what was believed to be an acute catarrhal jaundice. Liver and spleen were not palpated, bile pigments were not present in the urine, but urobilin was 4 plus. The purpura consisted of a few pin point hemorrhages on the legs and buttocks and the platelet count was never lower than 384,000. Van den Bergh reaction was prompt direct, with 2.8 mg. per cent of bilirubin. Bleeding, clotting, and clot retraction times were all within normal limits. The patient recovered completely.

The arthritic group contributes nothing from the point of view of platelet or liver deficiency.

The problem of principal interest presented by this case is the association of disease of the liver and spleen with platelet deficiency. Did the liver damage per se cause a destruction of the platelets, was the spleen responsible, or can the cause be sought in dysfunction of the entire reticulo-endothelial system? There was obvious liver damage present in the patient, evidenced by hepatomegaly, jaundice of a rather severe nature, and a marked discrepancy between the various liver function tests. Rosenberg [1] stated that in 10 cases of acute catarrhal jaundice there appeared to be no relationship between the degree of icterus in different patients and the amount of galactose excreted. He found that an extensive and very diffuse process is essential for an abnormal galactose output. This is based on the actual observation of liver sections of a severe case of intrahepatic jaundice, which had been studied clinically. An excretion of over three grams of galactose in the urine is generally accepted as abnormal.

The presence of large amounts of urobilin is further evidence of hepatic derangement since this pigment is normally converted into bilirubin by the liver and excreted as such in the intestinal tract. Normally the kidneys may excrete a small amount. In Rosenberg's 10 cases urobilin was present in the urine at one time or other. Darries [2] concluded that the presence of urobilin in the urine indicates intrahepatic jaundice, whereas its absence indicates an obstructive jaundice. This is in accord with present clinical conceptions.

Regarding the formed blood elements and their relationship to liver damage, several things are in evidence. It is generally found that blood fibrinogen is increased in cases of jaundice. Burke [3] reported an increase in values of blood fibrinogen in four cases of catarrhal jaundice. In addition he reported an increase of fibrinogen in 79 per cent of 43 jaundiced cases. Of these cases 20 gave evidence of hemorrhagic tendencies demonstrated by purpura, epistaxis, etc. Platelet studies in these cases were not recorded.

Platelet deficiency has been attributed to liver disease. Weil [4] reviewed 20 cases of liver disease, chosen arbitrarily. Eleven of these 20 cases showed platelet counts below 150,000. This was in association with decreased retractility of the clot and prolongation of the bleeding time. He made no explanation for the deficiency. King [5] reported an appreciable decrease of platelets in 20 per cent of 100 cases of portal cirrhosis. In this particular series he found jaundice in 50 per cent of the cases, a rather high figure.

Prothrombin, an essential element in the clotting process, was formerly believed to be entirely derived from a breakdown of blood platelets (Barker [6]). Recent studies by Quick [7] and others indicate that prothrombin deficiency is due to injury of the liver, in most cases. In the present case the finding of a relatively normal amount of prothrombin in the face of the marked platelet deficiency would not be in harmony with the former belief. Quick states that prothrombin deficiency is responsible for hemorrhage, yet the majority of jaundiced cases do not bleed. This he attributes to a wide margin of safety in the prothrombin content of the blood, in that 80 per cent of this factor may be depleted before the hemorrhagic tendency manifests itself. He attributes the depletion to the absence of bile salts and acids in the intestinal tract causing a faulty absorption of vitamin K. Repeated studies by many observers, including Carr,[8] Quick,[7] King,[5] Abrami,[9] reveal that blood fibrin, fibrinogen and calcium are usually normal in jaundice.

In the present case we must assume that rather widespread liver injury was present. There was gross enlargement of the organ, deep jaundice, and abnormal amounts of urobilin in the urine. Galactose was excreted in abnormal amounts, and the hippuric acid excretion was diminished. Bleeding and clotting times were decidedly prolonged above normal, but blood fibrinogen was normal. Clinically the case may be regarded as one of catarrhal jaundice, with anorexia, abdominal discomfort, slight fever, bilirubinemia and bilirubinuria.

It does not seem likely, however, that the liver injury per se was responsible for the thrombocytopenia. Abrami [9] stated that the liver is not the determining factor in the production of purpura. His view was based on the fact that in experimental lesions of the liver, prolonged bleeding time, thrombocytopenia and nonretractility of the clot do not occur. Capillary fragility, he does admit, is seen in severe icterus as in the advanced stage of all cirrhoses.

In this case there was also splenomegaly and some generalized lymphadenopathy, affecting chiefly the cervical glands. There is considerable evidence that the spleen plays an active part in the removal of platelets from the circulation. Splenectomy is the most effective form of therapy in essential thrombocytopenic purpura and is usually followed by a prompt rapid increase of platelets.

Of the few cases at the University Hospital all showed an appreciable rise averaging 400,000 in three days. Evans,[11] in a study of 11 cases following splenectomy, found a marked temporary rise and a slow fall to normal. In his cases of hemorrhagic purpura the peak was reached in eight days with a fall to normal in 10 to 20 days. In his cases of splenic anemia the maximum was reached in 15 days with a considerable decline in two to three weeks, and a normal count was reached after 100 days. As the platelet count rises, the bleeding time and retractility time of the clot shorten, with formation of a firmer and more effective clot. The degree to which coagulation is stimulated is not pro-

portional to the increase in platelets above a normal level, but it is substantial and may even cause death as a result of mesenteric or portal thrombosis.

The mechanism by which the spleen exerts this function is not known. Torrioli [10] isolated from the spleen and other organs a substance which injured the megakaryocytes of the bone marrow and indirectly caused a shortage of platelets. The organs varied in their content of this substance in the following order: thymus, spleen, lung, lymph nodes, liver, heart and skeletal muscle. This degree of activity is proportional to their content of reticulo-endothelial tissue.

Brill [12] reported a case of chronic hemolytic icterus with a marked thrombocytopenia showing improvement after splenectomy. He believed the spleen was primarily at fault, but suggested that the disease involves the whole reticuloendothelial system, bone marrow, liver and spleen.

On the basis of the foregoing evidence we may assume a diffuse derangement of the reticuloendothelial tissue, including the spleen, liver and lymph glands. The process certainly was initiated by an apparently typical catarrhal jaundice. Treatment probably had little effect in bringing about the complete recovery.

A search of the literature revealed very few reported cases showing thrombocytopenic purpura in association with catarrhal jaundice. One practically identical case was reported by Alt and Swank.[13] This patient also recovered.

Loeper and de Seze [14] reported the occurrence of purpuric spots on the legs and body in cases of secondary cancer of the liver. The bleeding time and clotting time were prolonged and clot retraction was delayed. They state that purpura may occur in any type of liver disease if liver function is seriously impaired.

Stone and Bunim [15] reported a case of a 27 year old pregnant woman who developed a peculiar purpuric eruption on the face after delivery. Jaundice appeared seven weeks later, and terminated in acute yellow atrophy. The relationship of the purpura to the jaundice seems questionable.

Jones and Minot [16] reported 26 cases of catarrhal jaundice, none of which showed purpura.

A review of the cases of purpura at the University Hospital revealed one mild case of purpura associated with catarrhal jaundice. The hemorrhagic tendency was slight and unassociated with platelet deficiency or liver damage. In the case of acute yellow atrophy which terminated fatally there were purpuric hemorrhages noted at autopsy.

Summary

1. A case is reported of thrombocytopenic purpura associated with catarrhal jaundice and impaired liver function.

2. It seems probable that the thrombocytopenia was not due directly to impaired liver function but to an associated disturbance of the reticuloendothelial tissue.

3. A search of the literature revealed only one similar case.

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A CASE REPORT OF CUTANEOUS LEPROSY WITH A BRIEF DISCUSSION OF THE CLASSIFICATION, TREATMENT, AND EPIDEMIOLOGICAL PORTENT *

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M. B., a 67 year old Russian Jew, was first admitted to the hospital May 26, 1937, with a simple fracture of the neck of the left femur following a fall. At this time he gave a history of dyspnea on exertion for many years, and a chronic cough for at least a year. The physical examination showed a short, thick-set, elderly man whose face was somewhat leonine and whose eyebrows were thin in the lateral thirds. The pupillary reflexes were normal. Both inferior turbinates were hypertrophied, especially the left. The pharynx was injected and the breath was fetid. His dental hygiene was poor and the tonsils were small and embedded. Many coarse moist râles were present at the lung bases. The heart was not enlarged and no murmurs or arrhythmias were present. The patient was seen by the ear, nose and throat consultant because of his chronic sinusitis and by the dentist for mouth hygiene. The rhinologic examination disclosed pus in the middle fossa of the left nostril, and evidences of chronic pansinusitis for which conservative treatment was recommended. A roentgenogram of the chest demonstrated a generalized bronchovascular thickening, and in the absence of any more definite roentgenological findings early bronchiectasis was considered. A non-hemolytic streptococcus and *Staphylococcus albus* were found by culture of the sputum. Except for negative Wassermann and Kahn reactions the remainder of the laboratory findings were insignificant as far as this report is concerned, and the patient was dismissed as cured of the fractured femur on August 10, 1937.

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From the Medical Services of the Presbyterian Hospital in Philadelphia.

Subsequently he was attended in the Medical and Surgical Out Patient Clinics irregularly and was referred early to the Ear, Nose and Throat Clinic since his nasal disease steadily progressed. The turbinates ulcerated and the nasal septum developed a lesion which eventually perforated. Two biopsies were taken from this lesion because of the suspicion of neoplasm, and the reports were as follows: July 1, 1938—subacute granulation tissue. December 30, 1938—chronic hypertrophic rhinitis.

The patient complained of pain in both arms and legs and, when the administration of salicylates was ineffectual, he was referred to the clinic for peripheral vascular diseases. There a provisional diagnosis of atypical Buerger's disease was made, but various recognized treatments for this condition failed to produce any therapeutic results. At this time, mostly on account of the typical facies, but especially since this was coexistent with lesions, it was decided that leprosy was most probably the correct diagnosis. Therefore, the patient was hospitalized on the medical ward for study May 28, 1939.

On this occasion examination revealed an elderly man obviously suffering pain on motion of the extremities. The face had a "lion-like" appearance owing to the nodular thickening of the skin of the nose, forehead, cheeks, and lobes of the ears. The mucous membranes of the nose and throat were congested and the pharynx was granular. Fetor oris was marked and there were numerous small ulcers in the roof of the mouth which extended also to the nares, and a perforation of the anterior portion of the nasal septum was present. The skin over the entire body was dry and there was a peculiar brownish color of the hands and feet. Many red spots about ½ cm. in diameter were seen over the body, as well as many scratch marks. A few coarse basal râles were found in the lungs, but the heart examination was normal. No masses or tender areas were felt within the abdomen, although there was a left indirect inguinal hernia. The hands and feet were quite tender to pressure, and the posterior tibial and dorsalis pedis arteries were not palpable on either side. The reflexes were hypoactive throughout.

The diagnoses were pediculosis corporis, left indirect inguinal hernia, avitaminosis and chronic upper respiratory disease. Leprosy and peripheral vascular disease were tentatively diagnosed. Slides were made by scraping the lesions of the mouth and nose with a dull scalpel, and these when stained with the acid-fast technic were found to be loaded with lepra bacilli. A biopsy was then made from a nodule in the skin of the face and this was reported by Dr. Philip Custer as follows:

"*Gross Description:* Specimen consists of small pieces of firm, white, blood-stained tissue.

"*Microscopic Description:* The nodule is covered by epidermis and is formed by inflammatory tissue of chronic granulomatous nature, with fibroblastic proliferation being rather markedly in evidence. In some areas a foamy quality to certain of the macrophages is evident. The smears from the cut surface of the first specimen show many acid-fast organisms which conform morphologically to the bacilli of leprosy. Similar organisms are recovered after centrifugation of a sample of blood.

"*Pathologic Diagnosis:* Leprosy. *B. leprae* recovered by deRivas method from blood."

As soon as the diagnosis was established the Public Health authorities were notified and it was discovered that this man's wife died of leprosy eight years previously. He had temporarily moved to another city and had avoided surveillance by the local Department of Public Health. Since his return, and without reporting the fact to us, he had attended various clinics in many local institutions, both before and concurrently with his visits to our clinics. In his peregrinations about the city for six years or more a great many physicians examined him in the various dispensaries and in the period of hospitalization for an unrelated condition, and all completely overlooked the diagnosis.

This sporadic case of leprosy has been of special interest inasmuch as failure to evaluate all the physical findings was responsible for delaying the diagnosis. During this time members of the community were exposed, for the patient mingled with others and even visited public baths regularly.

Discussion

The cardinal points for a diagnosis of leprosy are obtainable from standard textbooks of medicine, but the classification was revised at the Manila conference of the Leonard Wood Memorial for the Eradication of Leprosy, January 1931. The term "mixed type" was discontinued since the disease may be disseminated throughout the body and evidence of both the cutaneous and neural involvement is usually and probably always present. It was decided that the cases should be grouped upon the basis of the predominant lesions found, either neural or cutaneous. Provision was made for the "secondary neural cases," those in which the condition is resultant to irreversible damage to the nervous system but in which evidence of active disease processes can no longer be obtained by clinical methods.

At this same conference the term "cured" was discouraged and "arrested" was substituted to designate those cases in which there has been no positive clinical microscopic evidence of disease for a period of two years or more.

In the treatment of leprosy each case is managed individually and no single specific drug is employed. Particular attention is given to associated disorders that may determine the course of the disease and its therapeutic response. Various physiotherapeutic and chemical measures are used depending on the indication. The complications require appropriate medical, surgical, or orthopedic treatment as indicated. Preparations of oils of the chaulmoogra group have been most widely used. More recently Douglas Collier reports that diphtheria toxoid (formol) is now employed with encouraging results. It is possible that in time this may provide a method of treatment whereby the patient may remain at home, and it might be of great aid as a prophylaxis.

The presentation of this case of leprosy is especially timely since our soldiers are now fighting where this disease is more prevalent than in any other part of the world, and no doubt exposure will result with symptoms developing in some of the troops returning from this theater of war. Because of these facts our knowledge of the disease must be more thorough and the possibility of its occurrence must always be kept in mind.

It may be stated that the problem of leprosy will be interesting from the epidemiological standpoint, since we will be able to evaluate the incidence among those exposed and determine whether the impression that there is a familial tendency is tenable, and therefore whether segregation of those who are victims from members of their families should prevail. We will also be able to see whether racial resistance exists among the new exposures and whether the colored race is more resistant to the infection than the white race. Hitherto it has been difficult to determine the incubation period since the time of exposure was not known in many instances. However, if this disease develops in some of the returning soldiers a more definite impression may be gained as to the period required after exposure before the onset with its initial signs and symptoms. Likewise, it will be determined more conclusively whether a prolonged

exposure to the disease or single exposures to the more infectious skin types are responsible for the transmission.

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ACINAR CELL CARCINOMA OF PANCREAS: REPORT OF CASE IN WHICH FUNCTION OF CARCINOMATOUS CELLS WAS SUSPECTED *

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We are reporting a case of acinar cell carcinoma of the pancreas in which values for enzymatic activity in the serum were many times greater than those usually encountered in cases of carcinoma of the pancreas. These values were so high that we entertained the possibility that functioning of the acinar cell carcinoma contributed to their height.

Case Report

A man, aged 49 years, a Polish printer, was admitted to the Mayo Clinic September 9, 1940. During the preceding 10 years he had had an ulcerous type of dyspepsia which had been periodic, occurring in attacks of one to two weeks in length, once or twice yearly. Three months before his admission, an apparently typical attack of ulcerous dyspepsia had begun and had become by far the worst he had ever experienced; for the first time the pain had extended to his back and awakened him at night. The pain, which was relieved by food or soda, was still a major complaint at the time of his registration at the clinic. Two months before admission diarrhea had begun; the stools numbered two to four daily, were bulky, malodorous and light in color and floated on the water. Five weeks before admission, pain in both lower quadrants of the abdomen had begun. Three weeks before admission, the patient had noted swelling of the abdomen. At that time some anorexia developed but hardly enough to account for the loss of 40 pounds (18.1 kg.) which had taken place in the last three months.

On admission the patient did not appear to be acutely ill, but there was evidence of much loss of weight. Icterus was not present. Collateral venous circulation in the abdominal wall was not developed visibly. Palpation did not reveal the liver or the spleen or distention of the gall-bladder. There was slight ascites, but edema, peripheral or dependent, was not present.

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The value for hemoglobin was 13.1 gm. per 100 c.c., the erythrocytes numbered 4,600,000 and the leukocytes 10,500 per cubic millimeter of blood. The percentages of the various kinds of leukocytes were as follows: lymphocytes 18.5, monocytes 5, neutrophiles 74.5, eosinophiles 1 and basophiles 1. Morphologic study of the erythrocytes disclosed that they were slightly enlarged but that marked macrocytosis was not present. Routine urinalysis revealed albumin, graded 2; the results otherwise were negative. The results of routine flocculation tests for syphilis were negative as were roentgenograms of the thorax, the colon and the terminal portion of the ileum. One hour after the ingestion of eight arrowroot cookies and two glasses of water, 65 c.c. of gastric contents were recovered by tube; analysis of the contents disclosed that total acidity was 82, and free hydrochloric acid 76 (Töpfer's method). Roentgenographic examination of the stomach revealed a duodenal ulcer. The concentration of urea in the blood was 14 mg. per 100 c.c.; that of cholesterol in the plasma 181 mg. per 100 c.c., and that of bilirubin in the serum 1.1 mg. per 100 c.c.; the van den Bergh reaction was direct. The Quick prothrombin time was 25 seconds. The bromsulfalein test of hepatic function disclosed a dye retention of grade 3. The glucose tolerance test revealed a flat type of curve. Quantitative analysis of a single stool showed that 59.3 per cent (dry weight) was fat. Proctoscopic examination disclosed only internal and external hemorrhoids. The values for lipase and amylase in the serum were extremely high; they were respectively, 9.7 c.c. of twentieth-normal solution of sodium hydroxide for each cubic centimeter of serum and 4,000 units for each 1 c.c. of serum (method of Somogyi [1]) (figure 1).

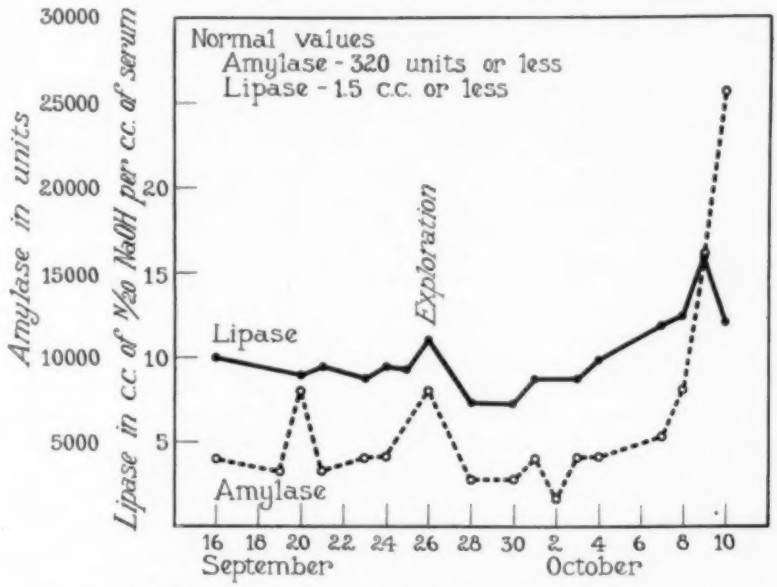

FIG. 1. Values for activity of lipase and amylase in the serum.

The tentative diagnosis was of penetrating duodenal ulcer with secondary pancreatitis. However, the marked loss of weight, the ascites, the steatorrhea and the extremely high values for enzymes in the serum were such unusual features that hospitalization of the patient for observation and preoperative preparation was proposed and carried out. A strict regimen for ulcer was instituted, but in spite of this measure, the pain continued. A low intake of fat controlled the diarrhea. The values

for lipoids in the plasma were low: cholesterol 151, cholesterol esters 111, lecithin 192, fatty acids 291 and total lipoids 442 mg. per 100 c.c. The values for lipase in the serum varied during the period from September 17 to September 25, inclusive, from 8.7 to 9.4 c.c. of twentieth-normal solution of sodium hydroxide for each cubic centimeter of serum and for amylase in serum from 3,200 to 8,000 units for each cubic centimeter of serum (figure 1). It became clear that the pain was not now of the ulcerous type and that the duodenal ulcer was not responsible for the patient's illness. The progressive character of the illness, the marked loss of weight, the steatorrhea and the sustained high levels of enzymatic activity heretofore observed only in neoplastic disease of the pancreas led[2] to diagnosis of carcinoma of the pancreas, and because of the exceedingly high level of enzymatic activity in the serum, the presence of a functioning acinar cell carcinoma was suspected.

An exploratory operation was performed September 26, 1940 through a midline incision. When the peritoneal cavity was opened, brownish ascitic fluid was disclosed, a large amount of which was aspirated and preserved for study. There were a number of metastatic nodules in the liver; a portion of one of these nodules was removed for microscopic examination, which revealed adenocarcinoma of grade 2. The pancreas had a rounded edge and was markedly indurated and thickened. This change was present throughout the gland, and seemed to be most marked in the head of the pancreas. All of the peritoneal tissues appeared to be congested as though they had been subjected to the action of some irritant. Small individual blood vessels were apparent over the entire peritoneum. It appeared likely that the primary lesion was in the pancreas, but inasmuch as metastasis had occurred already, extensive exploration did not seem justifiable, and the wound accordingly was closed.

A culture of the ascitic fluid did not reveal organisms. Values for lipase and amylase in the ascitic fluid were respectively 127 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter and between 50,000 and 75,000 units of amylase per cubic centimeter.

The patient's convalescence was uneventful. His pain persisted. The diarrhea was controlled fairly well with a low intake of fat. The ascites reformed partially. The values for lipase and amylase in the serum remained extremely high, reaching levels not observed by us previously in either benign or malignant neoplastic disease of the pancreas. The values for activity of lipase and amylase were respectively 15.8 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter of serum and 25,600 units per cubic centimeter of serum. A dextrose tolerance curve was again of the flat type. The patient was dismissed October 24, 1940.

Through the coöperation of the patient's family physician, we were informed of the development of jaundice, and of the painful and progressively downward course. The patient died February 27, 1941. With the coöperation of the patient's physician, the opportunity was given to examine the liver, pancreas, duodenum and stomach five days after death. In this interval, the tissues were preserved in dry ice.

Pathologic Examination of Specimen Obtained at Necropsy. A large, firm, nodular mass which was approximately 5 cm. in diameter was found in the head of the pancreas. On the cut surface the tumor was grayish white with numerous yellowish areas scattered over it (figure 2), it was very hard, and had a granular appearance. The mass had compressed and partially obstructed the common bile duct and the duct of Wirsung. Both of these ducts were greatly dilated proximal to the lesion.

On the anterior aspect of the body of the pancreas was a cyst-like structure which was approximately 4 cm. in length and 2.5 cm. in depth and in width (figure 2). It was densely adherent to the posterior wall of the stomach. Its contents consisted of greenish yellow fluid and crystals of ice. The wall was formed of fibrous tissue lined by yellowish gray, necrotic tissue. The splenic artery traversed the cavity and a por-

tion of the thrombosed splenic vein formed part of the wall. The wall of the splenic vein in this region appeared to be necrotic. No connection could be found between the dilated and tortuous duct of Wirsung and the cyst-like cavity. In the region of this structure there were several yellowish, softened areas.

The tail of the pancreas was somewhat fibrotic but was otherwise normal. The regional lymph nodes were enlarged and firm and on the cut surface appeared grayish white, homogeneous and granular.

The liver weighed 4,350 gm., and the normal contour was distorted by grayish nodular masses of varying sizes. The largest mass was present in the right lobe and measured 20 by 15 by 12 cm. The cut surfaces of these masses were grayish white and granular and had the appearance of metastatic carcinoma. The intervening hepatic parenchyma was deep green.

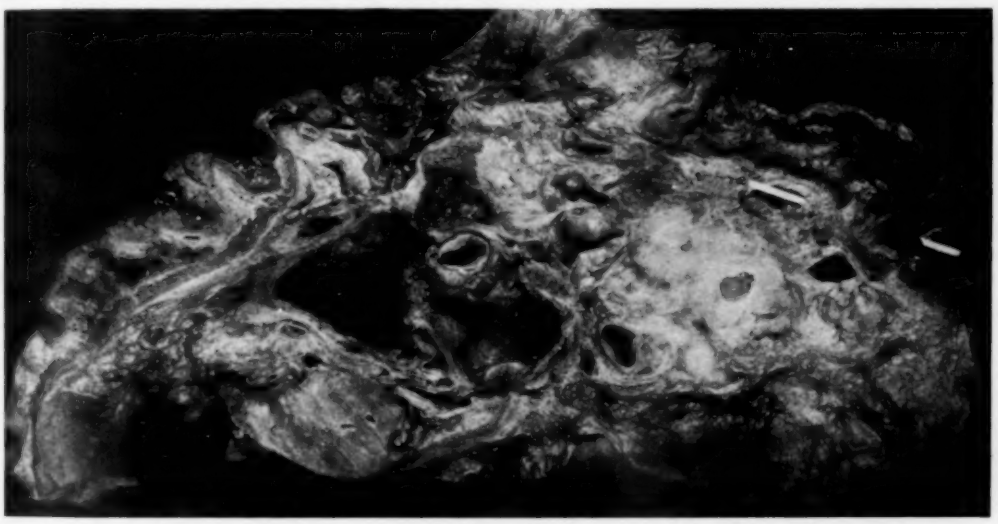

FIG. 2. Carcinoma of head of pancreas with probe in common bile duct. Note pseudocyst in body of pancreas with splenic artery transversing it.

The extrahepatic and intrahepatic bile ducts and the gall-bladder were dilated. The gall-bladder contained about 100 c.c. of bile and the wall appeared normal.

The stomach appeared normal but on the posterior wall of the duodenum there was a shallow chronic duodenal ulcer which measured 0.8 cm. in diameter.

Histologic Examination. Sections taken from the mass in the head of the pancreas revealed a cellular adenocarcinoma which was graded 2 (on the basis of 1 to 4, in which 1 is the least and 4 the most malignant). There was definite formation of acini by the neoplastic cells and the appearance was consistent with that of a carcinoma arising from the acinar tissue of the pancreas (figure 3*a*). The cells forming the acini were roughly pyramidal in shape. The cytoplasm of these cells was acidophilic except for a narrow zone in the basilar portion which was faintly basophilic with hematoxylin and eosin stains. The cytoplasm was vacuolated but zymogen granules could not be identified. Although the nuclei were hyperchromatic, mitotic figures were rare. Mucin could not be demonstrated by appropriate stains. In many regions of the carcinoma there was no evidence of tendency to form acini; the cells were present in solid masses separated by wide bands of fibrous connective tissue. The neoplastic cells in these regions generally were elongated in appearance. In some regions there was definite evidence of postmortem autolysis. The carcinoma had invaded the nor-

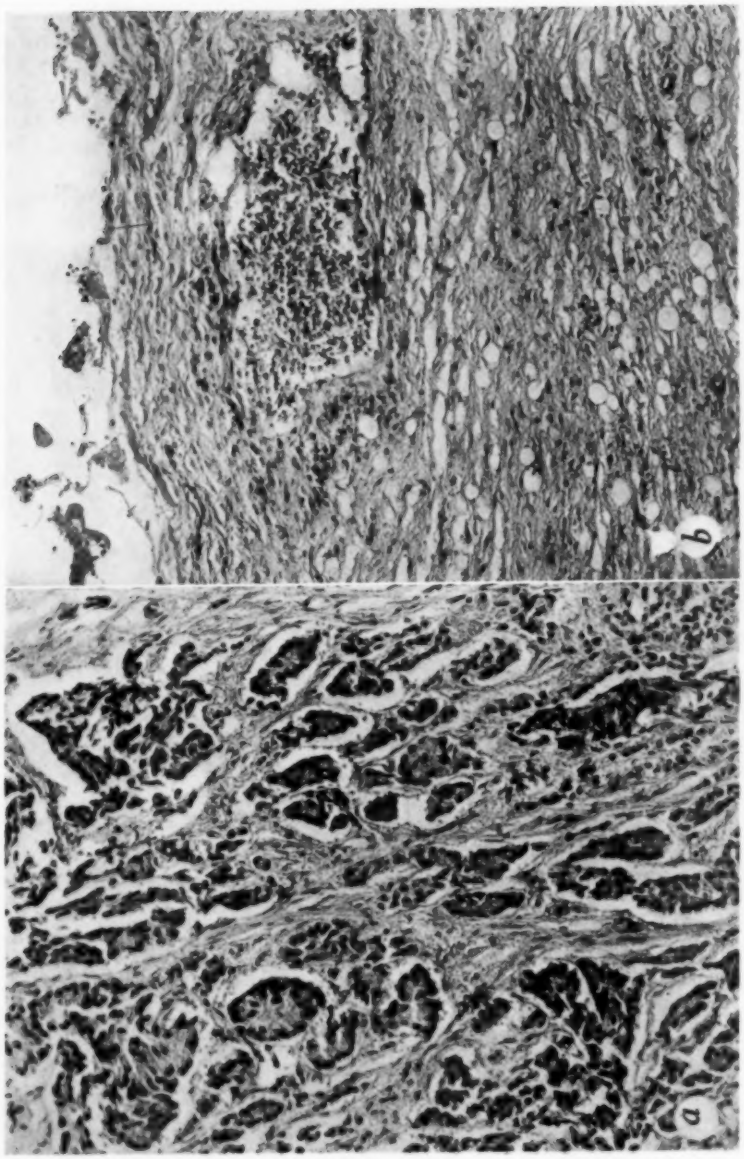

FIG. 3. Pancreas. *a*, Acinar carcinoma of head of pancreas. Note formation of acini (hematoxylin and eosin, × 160). *b*, Portion of wall of pseudocyst (hematoxylin and eosin, × 100).

mal parenchyma and resulted in destruction of the adjoining acinar tissue and the islands of Langerhans. In sections taken from the duct of Wirsung in the head of the pancreas, the neoplasm was found to have invaded the wall and almost completely obstructed the lumen.

The wall of the cyst-like structure was found to consist of fibrous, hyalinized, connective tissue without any evidence of an epithelial lining (figure 3*b*). On the inner surface of the wall there were patches of fibrin and necrotic debris. Included in the fibrous tissue wall there were macrophages containing lipoids and numerous collections of lymphocytes, many of which were perivascular. Deposits of hemosiderin and hematoidin also were present. Deep in the wall neoplastic cells were found in the perineural lymphatic structures. The surrounding parenchyma showed evidence of degeneration together with an interlobular fibrosis.

In addition to the large pseudocyst there were several smaller cyst-like structures which contained granular debris, fibrin and hematogenous pigments surrounded by a wall of fibrous connective tissue.

In the tail of the pancreas there was atrophy of the parenchyma with interlobular and intralobular fibrosis. Carcinoma could not be found in this portion of the pancreas and the ducts were dilated moderately.

In sections of the tumors in the liver, a cellular adenocarcinoma was discovered which appeared identical with the pancreatic carcinoma. The surrounding hepatic cells appeared compressed and atrophied and the sinusoids were dilated.

The following anatomic diagnoses were made: (1) Carcinoma of the head of the pancreas (acinar type), (2) metastasis to the liver and lymph nodes, (3) obstruction of the common bile duct with jaundice (clinically), (4) obstruction and dilatation of the duct of Wirsung with atrophy of the tail of the pancreas, (5) pseudocyst of the pancreas (residual of acute pancreatic necrosis) and (6) ascites.

Chemical Examination of Material Obtained at Necropsy. The activity of amylase was determined by the method of Somogyi and that of lipase by the method of Cherry and Crandall as modified by Comfort and Osterberg.[3]

Amylase was not demonstrated in either hepatic tissue or metastatic carcinoma of the liver. Values for amylase in pancreatic tissue removed from the region of the head of the pancreas, in fluid removed from the cyst, and in the ascitic fluid were respectively 400 units per gram, 1066 units per cubic centimeter and 520 units per cubic centimeter.

Values for lipase in hepatic tissue, metastatic carcinoma of the liver, and tissue from the head of the pancreas were respectively 7.0 c.c., 6.0 c.c., and 8.0 c.c. of twentieth-normal solution of sodium hydroxide per gram. Values for lipase in fluid removed from the pancreatic cyst and in the ascitic fluid were respectively 23.3 c.c. and 1.0 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter of fluid. It is worthy of note that the values for amylase and lipase in the ascitic fluid removed at necropsy were much less than those in the ascitic fluid removed at operation.

Comment

From the pathologic findings it seems reasonable to attribute the regions of necrosis and the formation of the pseudocysts in the body of the pancreas to attacks of acute pancreatic necrosis secondary to neoplastic obstruction of the duct of Wirsung. In retrospect the more severe attacks of pain may well have been the result of such attacks of acute pancreatic necrosis. At the time of necropsy the duodenal ulcer did not appear to have been very active.

The nature of the carcinoma does not appear questionable. It was clearly of the acinar cell type. The source of the large amounts of amylase and lipase in the blood and in the ascitic fluid is the chief point of interest.

Several explanations may be advanced for the high values for enzymatic activity in this case. First, the high values were due to obstruction of the pancreatic ducts by the carcinoma. Experimentally, in dogs, ligation of the pancreatic ducts is followed by a rise in values for enzymatic activity in the serum. The obstruction increases the intraductal pressure, ruptures the small radicles of the pancreatic ducts, permits pancreatic juice to enter the lymphatics and ultimately the blood stream. The values return to normal in from 10 to 14 days, presumably because the obstructive pancreatitis subsides and secretion is suppressed. In man, elevated values for lipolytic activity of the serum have been found in 40.5 per cent and for amylolytic activity of serum in 8 to 22 per cent of cases of carcinoma of the pancreas. We may assume that obstruction of the pancreatic ducts by carcinoma of the pancreas produces the elevated values for enzymatic activity in the serum in a manner similar to that in experimental ligation of the ducts-and that elevated values are not present in all cases because the carcinoma does not obstruct the ducts in all cases and because obstruction of the duct finally destroys the acinar structures which are the source of enzymatic activity, permitting the values to return to normal. Second, in this case, pancreatitis was responsible for the high values for activity of enzymes in the serum. Pancreatitis had undoubtedly been present at some time during the course of the disease. The inflammatory pseudocysts, we believe, were the residue of pancreatic necrosis. The pancreatitis was the result of obstruction and might have been responsible at one time for the elevation in the values for enzymatic activity in the serum along with the obstruction of the ducts. Third, absorption through the walls of the inflammatory cysts and of the blood vessels traversing the cavity of the cyst contributed to the high values for enzymatic activity in the serum. Although this factor must be considered, it may be pointed out that the cysts are not known to have been present at the time the high enzymatic activity was found in the serum and the ascitic fluid. At least, such cysts were not found at the time of surgical exploration.

The values for enzymatic activity in the serum in this case were higher than those previously seen in other cases of carcinoma of the pancreas. In Comfort and Osterberg's series of cases of carcinoma of the pancreas, an occasional value of 6 or 7 c.c. of twentieth-normal sodium hydroxide per 1 c.c. of serum for lipolytic activity has been observed, but usually the values have been in the range of 2 to 4 c.c. of twentieth-normal sodium hydroxide per cubic centimeter of serum, while the values for amylase as a rule have been less than 1,000 units. Values for lipolytic activity of 9 to 10 c.c. of twentieth-normal sodium hydroxide per 1 c.c. of serum and for amylase of 4,000 to 8,000 units per cubic centimeter of serum were obtained consistently in this case; the values were so much higher than those previously encountered that we wondered whether obstruction of the duct by carcinoma and secondary pancreatitis constituted adequate explanation for the high values for enzymatic activity in the serum and whether some other factor was contributing to the high values. Later, when values for lipolytic activity reached 15.8 c.c. of twentieth-normal sodium hydroxide per 1 c.c. of serum and for amylase 25,800 units per cubic centimeter of serum, we were ready to believe that some other factor was contributing to the exceedingly high values. It occurred to us that a functioning acinar cell carcinoma of the pancreas might be the additional factor. Demonstration that high values persisted throughout life would have furnished strong evidence that the carcinoma of the

pancreas was functioning, because values elevated by obstruction of the pancreatic duct should have returned to normal as atrophy of the acinar structures of the pancreas progressed and probably would have returned to normal long before the patient's death. Unfortunately, we could not carry out such determinations.

Although examination of the material obtained at necropsy showed that the carcinoma was of the acinar cell type, chemical examination of the metastatic nodules in the liver for amylolytic and lipolytic content did not furnish the evidence that we sought, to show that the carcinoma was functioning; namely, that metastatic carcinoma contained enzymes in quantities greater than the parenchyma of the liver in which the nodules were embedded.

We do not believe that functioning of the acinar cell carcinoma should be discarded as an accessory cause of the high values in this case because of the absence of chemical proof. It is possible that the content of enzymes in the tissues examined was altered profoundly during the five days which elapsed between the death of the patient and examination of the tissues. It is not unlikely that acinar cell carcinomata of the pancreas do function and produce high values for enzymatic activity in the serum. In support of this probability it may be pointed out that many neoplasms carry on some of the functions of their parent cells. Especially is this true of certain tumors arising from the endocrine glands such as the suprarenal glands, the ovaries and the pituitary body, as well as carcinoma of the islands of Langerhans. Carcinoma arising from glandular organs is also known to function, as evidenced, for example, by the mucin and pseudomucin produced in numerous adenocarcinomata, the production of bile by hepatomata and of colloid by carcinomata of the thyroid gland. Ewing [4] stated that chemical studies support the belief that some cancerous tissues are capable of carrying on cellular function, as shown by the high content and qualities of lipoids in hypernephroma and the considerable content of iodine in thyroid carcinoma. He demonstrated that as a rule functional activities diminish with increasing anaplasia and that original overactivity then is succeeded by complete failure, as in the pigment-free metastatic lesions of melanoma.

Summary

In this case of acinar cell carcinoma of the pancreas the values for lipolytic activity and particularly for amylolytic activity in the serum and the ascitic fluid were exceedingly high. Various explanations of the high values have been considered. It is possible that the high values were owing entirely to obstruction of the pancreatic ducts, to the obstructive pancreatitis or to absorption of enzymes from the pancreas and the pseudocyst. The values for enzymes were so much higher, however, than in any other case of carcinoma of the pancreas observed by us, that an explanation other than these was sought. The possibility that the high values were due to functioning of the acinar cell carcinoma was examined and, although the data have been too incomplete to warrant the conclusion that the carcinoma was functioning, the possibility is an attractive one that deserves consideration in future cases of carcinoma of the pancreas with high values for amylolytic and lipolytic activity in the serum. The case has been reported to call attention to the possibility that acinar cell carcinomata of the pancreas may function and may be responsible for high values for enzymatic activity in the serum.

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3. COMFORT, M. W., and OSTERBERG, A. E.: Serum amylase and serum lipase in the diagnosis of disease of the pancreas, Med. Clin. N. Am., 1940, xxiv, 1137.
4. EWING, JAMES: Neoplastic diseases, Fourth edition, 1940, W. B. Saunders Company, Philadelphia, p. 38.

EDITORIAL

FAILURE OF THE VENOPRESSOR MECHANISM AS A FACTOR IN THE DEVELOPMENT OF SHOCK

THE importance of the rôle of the venopressor mechanism in maintaining the circulation has become generally known in large part through the work of Henderson and his associates. Henderson[1] has recently summarized his conceptions of this mechanism and the significance of its failure in the production of shock.

Maintenance of a normal circulation (i.e., a normal minute-volume output by the heart) depends not merely upon an effectively functioning myocardium but also upon the delivery through the veins to the right side of the heart of a quantity of blood sufficient to fill the cavities. There had long been difficulty in explaining satisfactorily the mechanical factors which bring about the return flow of an adequate volume of blood through the veins. The valves in the veins serve an important function in determining the direction of flow and preventing any reflux back into the tissues. Manifestly they do not contribute any positive force to the circulation. There is also a small positive pressure in the venous end of the capillaries and venules which, in conjunction with an intrathoracic pressure which is slightly below the atmospheric pressure, propels blood toward the heart. This vis-a-tergo, however, is relatively slight and seemed scarcely an adequate explanation, particularly in conditions in which the blood flow is accelerated.

Henderson has shown that an important contributing force is provided by the contractions of the skeletal muscles. As has been pointed out by Krogh, there is an abundant anastomosing network of arterioles, capillaries and venules interspersed between the muscle fibers. The veins are abundantly provided with valves which permit blood to flow only toward the heart. These vessels are filled with blood during periods of muscular relaxation, but during contraction of the muscle fibers, the increase in girth of the fibers, associated with their shortening, exerts pressure on the vascular network and vigorously propels blood onward into the veins. This action is compared to that of a peripheral or "booster" pump, which powerfully supplements the relatively feeble vis-a-tergo supplied by the cardiac contractions and the arterial pressure. This mechanism evidently must play a vital part in securing adequate return flow to the heart during periods of intense muscular activity when the rate of blood flow may be increased even to five times the resting rate.

Even in periods of muscular rest, however, Henderson believes this same force is operating and is equally important in maintaining a normal circulation. During health there is never complete relaxation of the muscles. Even when the body is as completely at rest as possible, the muscles are con-

[1] HENDERSON, Y.: Tonus and the venopressor mechanism: the clinical physiology of a major mode of death, Medicine, 1943, xxii, 223–249.

tinuously in a state of partial contraction or "tonus." This tonus is maintained by stimuli coming through the motor nerves from the motor nuclei of the spinal cord and bulb. During rest only a few of the muscle bundles are contracting at a given moment, but the successive contraction and relaxation of the muscle bundles exert a similar booster action that differs only quantitatively from that accompanying voluntary contraction.

As one proof of these contractions Henderson has cited the presence of action currents in electromyograms of resting muscles, and the increase in amplitude of these currents when measures are taken to increase the muscle tonus.

Henderson has devised a simple clinical procedure for determining the effectiveness of the venopressor mechanism and the adequacy of the venous blood return. The subject is placed, head down, on a table tilted at an angle of 45°. The arm is held vertically, and the height of the column of blood in the distended veins is measured. In patients with grave illness he was able to demonstrate a progressive lowering of this blood column as death approached. He thinks this is a more valuable indication of the need of plasma injections in shock than arterial blood pressure or estimations of venous pressure in the recumbent position.

The degree of muscle tonus and its accompanying "booster" action depends upon the "tone" of the spinal motor centers. This, in turn, is affected by a multitude of factors, mental, physical and chemical. It is much affected by respiration and by the concentration of carbon dioxide in the blood. Inhalation of carbon dioxide increases the tonus. Hyperventilation and pumping out of carbon dioxide (acapnea), on the other hand, lower tonus, reduce the effect of the booster pumps, and slow the return flow of blood to the heart, with resulting circulatory failure if it is too long continued.

Any serious impairment of the general health may reduce the tone, which Henderson speaks of as an "index of vitality." It is much reduced in the physical depression which accompanies serious acute or chronic illness, increasingly so as death is approached. Henderson believes that the "peripheral circulatory failure" which is the immediate cause of death in such conditions is not dependent upon loss of vasomotor tone, but upon inadequate return flow of blood to the heart which results from failure of this venopressor mechanism.

The pain and shock following physical injury or operation also diminish the "normal tonic function" of the motor centers. Henderson believes that the circulatory failure which accompanies shock may also be explained by a failure of the venopressor mechanism rather than by relaxation of the peripheral vessels following exhaustion of the vasomotor center. "When the tonic influence of the motor centers fails, the skeletal musculature becomes flaccid. Because of this flaccidity, the intramuscular pressure falls; the capillary pumps cease to operate; and the venous return to the heart diminishes until it becomes insufficient to allow the heart to maintain the

arterial blood stream and pressure. So the first, or circulatory stage of shock develops."

As the rate of blood flow falls, the oxygen requirement of the tissues is not met, and tissue asphyxia results. Seepage of the plasma from the capillaries then sets in, with progressive decrease in blood volume, further slowing of the circulation, and finally an abrupt fall in arterial blood pressure.

In animals intravenous administration of large amounts of fluid at this stage will restore the blood pressure and pulse amplitude, indicating that the circulatory collapse was not due to failure of the heart or vasomotor system. Saline solution will restore the circulation temporarily, but plasma is far more efficient.

Henderson believes that leakage of plasma from the vessels is due more to tissue asphyxia than to loss of plasma protein. This is based on plasmapheresis experiments, in which severe protein depletion was produced without any loss of fluid from the vessels provided the red cells were replaced and anoxemia avoided. He thinks the late manifestations of posthemorrhagic shock are also a result of tissue asphyxia, and strongly advocates transfusions of whole blood rather than merely plasma in such cases. This is also in accordance with the recommendations of the British War Office.

Henderson points out that this conception of shock eliminates the old puzzling question, "when the circulation fails without a hemorrhage, where has the blood gone?" It is not necessary to assume that the blood is pooled in the splanchnic vessels or in any other unusual location. "It simply slows and then stops circulating." It is to be found "essentially where it was when flowing . . . and the asphyxial tissues absorb the plasma."

Henderson emphasizes the rôle of carbon dioxide in controlling this venopressor mechanism. Both at rest and during muscular exertion "the amount of carbon dioxide produced in the tissues and carried by the blood to the central nervous system determines the tonic influences of the motor centers upon the muscles, and so the activity of their booster pumps and the volume of the venous return." It "determines alike the volume of the air breathed, the volume of the venous return and thereby the volume of blood circulated." Vasomotor reactions, on the other hand, are mainly concerned with adjustment of the arterial pressure and the distribution of the blood in the arterial system.

Without attempting an extensive discussion of this controversial question, it must be pointed out that Henderson's views as a whole have not been generally accepted. Many investigators feel that he has overemphasized the rôle of hyperpnea and acapnea in the production of shock, and has underestimated the importance of loss of fluid from the vessels. His work, in any case, is highly stimulating, and he has made many contributions of major importance to this subject. There can be little doubt that the venopressor mechanism is an important factor in maintaining and regulating the rate of blood flow.

REVIEW

Practical Survey of Chemistry and Metabolism of the Skin. By MORRIS MARKOWITZ, M.D. 196 pages; 13.5 × 20.5 cm. The Blakiston Company, Philadelphia. 1942. Price, $3.50.

To the reviewer's knowledge, this monograph is the only essay of its kind in publication and covers the subject of chemistry and metabolism of the skin succinctly and quite fully within the limits of the space available.

The author should not permit himself the liberty of dealing in probabilities as, for instance, on page 23, where he states "The probability is that it (hyperglycemia) is a hepato-pancreatic disturbance or a metabolic disorder." He also states on page 21, "Predisposition to certain dermatoses may also be caused by carbohydrate intake by producing an excessive secretion of fat in the skin and carbohydrate excretion in the sweat." To make such a statement is begging the question. There are several more similar statements as on page 47, "Vitamin C is probably a catalyzing enzyme." And on page 71, "moist compresses and fomentations may produce spread of infection."

Aside from this and several other similar statements, the book is worth careful reading. I would hesitate, however, to accept this statement: "Dermatologically it (panthothenic acid) is of interest as an anti-gray hair factor and antidermatitic."

H. M. R.

BOOKS RECEIVED

Books received during September are acknowledge in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Ear, Nose and Throat in the Services. By R. SCOTT STEVENSON, M.D., F.R.C.S., Ed.; Major R. A. M. C. 116 pages; 17 × 11 cm. 1943. Oxford University Press, New York. Price, $1.50.

Microscopic Technique in Biology and Medicine. By E. V. COWDRY, Professor of Anatomy, Washington University. 206 pages; 23.5 × 16 cm. 1943. The Williams and Wilkins Company, Baltimore. Price, $4.00.

Nervousness, Indigestion and Pain. By WALTER C. ALVAREZ, M.D. 488 pages; 24.5 × 16.5 cm. 1943. Paul B. Hoeber, Inc., New York. Price, $5.00.

War Endocrinology. By JAMES H. HUTTON, M.D. 363 pages; 23.5 × 16 cm. 1943. The Wayside Press, Chicago.

Synopsis of Tropical Medicine. By SIR PHILIP MANSON-BAHR, C.M.G., D.S.O., M.D., F.R.C.P. 224 pages; 19 × 12.5 cm. 1943. Williams and Wilkins Company, Baltimore. Price, $2.50.

Primeras Reuniones Extraordinarias de la Asociación de Médicos del Hospital Durand. Two volumes. 1428 pages; 23.5 × 16.5 cm. 1942. Caporaletti Hnos., Buenos Aires.

La Prueba Intradérmica de Giroud en la infección tifoexantemática. Nuestra Experiencia Personal. Técnicas y Posibilidades de su Aplicación. By G. CLAVERO and F. PÉREZ GALLARDO. 65 pages; 24 × 17 cm. 1942. (Publicaciones de la Revista de Sanidad e Higiene Publica.) Imprenta de J. Cosano. Madrid.

Investigación del virus tifoexantemático en las ratas de España. By G. CLAVERO and F. PÉREZ GALLARDO. 25 pages; 24 × 17 cm. 1943. (Publicaciones de la Revista de Sanidad e Higiene Publica.) Imprenta de J. Cosano. Madrid.

Tifus Exantemático. Etiología, Clínica, Profilaxis. By G. CLAVERO and F. PÉREZ GALLARDO. 166 pages; 25 × 17.5 cm. 1941. Gráficas Afrodisio Aguado, S.A., Madrid.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,482 Fellows and Associates of the College on active military duty. Herewith are reported the names of 7 additional members, bringing the grand total to 1,489.

James E. Bovaird
James H. Danglade
Herbert K. Ensworth
Warren M. Gilbert
Lester D. Watson
John C. White
Bertrand O. Woods

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. H. Sheridan Baketel, Jersey City, N. J.
Dr. Constantine P. Faller, Harrisburg, Pa.
Dr. Harold G. Trimble, Oakland, Calif.

Gifts to the College Library

The following gifts to the College Library of Publications by Members are gratefully acknowledged:

Dr. Truman G. Schnabel, F.A.C.P., Philadelphia, Pa.—"The Scope of 1942," University of Pennsylvania School of Medicine Yearbook.

Reprints

John E. Garcia (Associate), Lieutenant, (MRC), U. S. Army—1 reprint;
Bernard A. Goldman (Associate), Lieutenant, (MRC), U. S. Army—1 reprint;
Dr. Arthur J. Logie, F.A.C.P., Miami, Fla.—1 reprint;
R. Bruce Logue (Associate), Major, (MRC), U. S. Army—1 reprint;
Dr. Bernard J. McCloskey (Associate), Johnstown, Pa.—1 reprint;
Dr. Frederick W. Mulsow, F.A.C.P., Cedar Rapids, Iowa—1 reprint.

Third Annual Schering Award Competition

The third nation-wide competition for the Schering Award is now open. Three major prizes of a total value of $1,000 will be awarded to undergraduate medical students who submit the best critical dissertations on the subject, "Hormones and Cancer." As in previous years, the Judges for the Schering Award will include outstanding American investigators in the fields of endocrinology, medicine and chemistry.

The Schering Award was established by the Schering Corporation in 1941, for the purpose of encouraging a wider interest in current endocrinological developments among undergraduate medical students. The competition is sponsored and administered by the Association of Internes and Medical Students, and participation is limited to undergraduate medical students in the United States and Canada. It is noted that all manuscripts must be submitted no later than January 15, 1944. Communications should be addressed to "The Interne," 7 East 42nd Street, New York 17, N. Y.

The fifth painting in the famed "Pioneers of American Medicine" series sponsored by John Wyeth & Brother, and entitled "The Father of American Pharmacy," was unveiled at ceremonies November 5 during National Pharmacy Week in Philadelphia. The painting depicts William Procter (1817–1872) studying a formula for the standardization of drugs while at work with an assistant in his laboratory. The principal speaker was Dr. Ivor Griffith, Ph.M., Sc.D., F.R.S.A., President of the American Pharmaceutical Association and of the Philadelphia College of Pharmacy and Science.

Dr. Charles F. McKhann, F.A.C.P., Professor of Pediatrics and Communicable Diseases at the University of Michigan Medical School, has resigned to accept a position as Assistant to the President of Parke, Davis and Company of Detroit. Dr. McKhann will devote his time entirely to the scientific activities of the company. He assumed his duties October 15.

Since 1930, he has conducted and directed research on communicable diseases, immunology, renal diseases, nutritional diseases, and on certain phases of toxicology. He developed and introduced immune globulin and has contributed to the development of several other products.

The Medical Society of the State of Pennsylvania conducted its 93rd Annual Session in Philadelphia, October 5–7, under the Presidency of Dr. Augustus S. Kech, F.A.C.P., of Altoona. Among the guest speakers was Dr. Wallace M. Yater, F.A.C.P., Washington, D.C., whose subject was "Selection and Interpretation of Laboratory Procedures."

The Kansas City Annual Fall Clinical Conference was held in Kansas City, October 4–6, 1943, under the Presidency of Dr. James E. Stowers. Many distinguished authorities from various parts of the country appeared on the program, including Dr. Paul D. White, F.A.C.P., Boston, Dr. E. H. Rynearson, F.A.C.P., Rochester, Minn., Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., and Dr. Harrison F. Flippin, F.A.C.P., Philadelphia.

One evening was given over to a panel discussion of "Navigating the Medical Future," which included discussions of the Wagner-Murray Senate Bill No. 1161, which would impose compulsory health insurance; improvements in the standards of medical education and the influences that may jeopardize these standards in the regimentation of medical students; the group hospitalization plan of voluntary prepayment for medical services that is in operation in the Jackson and Wyandotte County Medical Societies; methods now used in many Kansas counties for payment of medical services for indigent and low income groups; the American philosophy of private enterprise as the best means of promoting a prosperous peace and maintaining the integrity of American life and happiness; and the program for medical care favored by the American Federation of Labor.

Dr. Nathan S. Davis, F.A.C.P., Chicago, Assistant Professor of Medicine at Northwestern University Medical School, was the recipient of the Distinguished Service Award of the Mississippi Valley Medical Society for 1943. The award, consisting of a gold medal and certificate, was presented to Dr. Davis by the Society's President, Dr. Edward M. Myers, at Quincy, Ill., September 30, during the 9th Annual Meeting of that Society. The citation reads, "A high type of physician, an able clinician, a very accurate investigator and last but not least, a writer of syndicated medical advice for the public. While he descends from an illustrious family in medicine, he has carved his own niche in the profession."

Dr. M. Fernan-Nunez, F.A.C.P., Professor of Pathology in the Marquette University Medical School, Milwaukee, toured South Dakota from September 19 to 26, giving lectures on tropical diseases to medical groups in Aberdeen, Huron, Sioux Falls, Pierre, Rapid City and Fort Meade. Soldiers and sailors returning from tropical service, and tourists coming back from vacations in the southern states and Mexico, are bringing into northern latitudes an increasing amount of exotic diseases, especially malaria. Dr. Fernan-Nunez' trip was sponsored as a joint project of the South Dakota State Board of Health and the United States Public Health Service to bring the latest developments in the field of tropical medicine to the medical profession of that state.

Dr. M. Fernan-Nunez also lectured to the medical officers of Camp McCoy, Wis., September 6, on "Malaria," as a member of the national faculty of War-Time Graduate Medical Meetings.

The Mead Johnson Vitamin B Complex Award

Nominations are solicited for the 1944 award of $1,000 established by Mead Johnson and Company to promote researches dealing with the B complex vitamins. The recipient of this award will be chosen by a committee of judges of the American Institute of Nutrition. The award will be given to the laboratory (nonclinical) or clinical research worker in the United States or Canada who, in the opinion of the judges, has published during the previous calendar year January 1 to December 31 the most meritorious scientific report dealing with the field of the B complex vitamins. While the award will be given primarily for publication of specific papers, the judges are given considerable latitude in the exercise of their function. If in their judgment circumstances and justice so dictate, it may be recommended that the prize be divided between two or more persons. It may also be recommended that the award be made to a worker for valuable contributions over an extended period but not necessarily representative of a given year. Membership in the American Institute of Nutrition is not a requisite of eligibility for the award.

To be considered by the committee of judges, nominations for this award for work published in 1943 must be received by the secretary, Arthur H. Smith, Ph.D., Wayne University College of Medicine, Detroit, by Jan. 10, 1944. The nominations should be accompanied by such data relative to the nominee and his research as will facilitate the task of the committee of judges in its consideration of the nomination.

Major R. Bruce Logue (Associate), MRC, U. S. Army, Chief of Cardiovascular Section of Lawson General Hospital, Atlanta, Ga., gave the A.O.A. address at Emory University Medical School on September 17, 1943. The title of the address was "Neurocirculatory Asthenia."

Dr. James E. Paullin, Atlanta, Ga., President, A.C.P., addressed the 37th Annual Meeting of the Southern Medical Association held in Cincinnati, November 16–18.

Dr. Joseph J. Combs, F.A.C.P., Raleigh, N. C., was elected Treasurer of the North Carolina Tuberculosis Association at a recent meeting.

Dr. Jerome E. Andes, F.A.C.P., former instructor in the West Virginia University School of Medicine and more recently Medical Director of the Hercules Powder Company, Lawrenceville, Kan., has returned to Morgantown to become Director of the Student Health Center at the University.

Dr. Newton G. Evans, F.A.C.P., Dean of the College of Medical Evangelists, Los Angeles, has been elected President of the Alumni Research Foundation of that institution, which has been incorporated under the laws of California for the primary purpose of stimulating research.

Captain Henry L. Dollard, F.A.C.P., (MC), U. S. Navy, Senior Medical Officer of the Ninth Naval District, Great Lakes, Ill., presided over a panel discussion on "War Medicine and Surgery" conducted in connection with the Eleventh Annual Assembly of the Omaha Mid-West Clinical Society, October 25–29.

Among guest speakers on the program were Dr. Harold G. Wolff, F.A.C.P., New York, N. Y., "Headache Mechanisms"; Dr. Sara M. Jordan, F.A.C.P., Boston, "Functional Diseases and the War"; and Dr. Tom Spies, F.A.C.P., Birmingham, Ala., "Detailed Methods of Diagnosis and Therapy in Acute Nutritive Failure."

Dr. Wesley W. Spink, F.A.C.P., Minneapolis, is Secretary of the American Society for Clinical Investigation.

Dr. Roger I. Lee, F.A.C.P., Boston, addressed the second Profession-Industry Follow-Up on the National Conference on Planning for War and Postwar Medical Services at the Waldorf-Astoria Hotel in New York City, October 4, his title being "Medicine's Position and Policy."

Under the Presidency of Dr. Waller S. Leathers, F.A.C.P., Dean of Vanderbilt University School of Medicine, Nashville, Tenn., the 54th Annual Meeting of the Association of American Medical Colleges was held in Cleveland, October 25–27. Among speakers on the program were Brigadier General George F. Lull, F.A.C.P., U. S. Army, "The Army Specialized Training Program"; Commander Bartholomew W. Hogan, F.A.C.P., U. S. Navy, "The Navy V 12 Program"; Dr. Willard C. Rappelye, F.A.C.P., New York City, "Postwar Planning for Medical Education"; Dr. Joseph T. Wearn, F.A.C.P., Cleveland, "Present Methods of Medical Teaching"; Dr. Carl J. Wiggers, F.A.C.P., Cleveland, "Correlation of Physiology Instruction with War Problems."

Dr. Russell M. Wilder, F.A.C.P., has resigned as Chief of the Civilian Food Requirements Branch of the Food Distribution Administration, Washington, and will resume his activities at the Mayo Clinic, Rochester, Minn.

Brigadier General Eugen G. Reinartz, F.A.C.P., of the U. S. Army, addressed the 15th Annual Meeting of the Aero Medical Association of the United States at Cincinnati, October 26–27.

The University of Illinois recently accepted a grant of $25,000 a year for three years from the Upjohn Company, Kalamazoo, Mich., for the study of penicillin in their Biochemistry Department at Urbana.

Major General James C. McGee, F.A.C.P., formerly Surgeon General of the U. S. Army, recently addressed the faculty and students of New York University College of Medicine on the subject of military medicine, with particular reference to tropical diseases.

Brigadier General Charles C. Hillman, F.A.C.P., U. S. Army, addressed the Medical Society of Virginia at Roanoke, October 25–27, on "Medical Operations in the Pacific Theaters."

Dr. Abraham H. Aaron, F.A.C.P., Buffalo, N. Y., was a speaker on the program devoted to the art and science of therapeutics at the 93rd Annual Session of the Medical Society of the State of Pennsylvania, Philadelphia, October 5–7.

Dr. Theodore G. Klumpp, F.A.C.P., who is now President of the Winthrop Chemical Company, has been elected a member of the Academia de Ciencias Medicas, Fisicas y Naturales de la Habana, Cuba.

Among guest speakers and lecturers who participated in giving the Alumni Association Refresher Course of the Medical College of the State of South Carolina, Charleston, November 3–4, were Dr. George W. Thorn, F.A.C.P., Boston, "Physiologic Considerations in the Treatment of Nephritis"; Dr. Harrison F. Flippin, F.A.C.P., Philadelphia, "The Uses and Abuses of the Sulfonamides"; Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, "Differential Diagnosis of the Anginal Syndrome"; Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, "Deficiency Diseases."

Dr. Oscar Lotz, F.A.C.P., Milwaukee, and Dr. John H. Skavlem, F.A.C.P., Cincinnati, have been elected Vice President and Secretary-Treasurer, respectively, of the Mississippi Valley Trudeau Society.

Dr. Felix Hurtado, F.A.C.P., Havana, Cuba, was a guest speaker on the program of the 72nd Annual Meeting of the American Public Health Association, New York City, October 11–14.

Dr. Walter A. Bastedo, F.A.C.P., New York City, was Chairman of a panel discussion on "Use of Sulfonamides in Gastrointestinal Diseases" under the auspices of the Sixteenth Graduate Fortnight of The New York Academy of Medicine, October 19.

The War-Time Graduate Medical Meetings Committee has announced the rapid growth and expansion of the programs being given at Army and Navy hospitals and installations all over the United States and, in some instances, in Canada. These meetings are under the joint auspices of the American College of Physicians, the American Medical Association and the American College of Surgeons.

Under the Chairmanship of Dr. James J. Waring, F.A.C.P., a three-day course of meetings was given at the Fitzsimmons General Hospital and at the University of Colorado and the Colorado General Hospital, Denver, September 30–October 2.

Under the Chairmanship of Dr. E. L. Henderson, Louisville, and his Committee consisting of Dr. Chauncey W. Dowden, F.A.C.P., Louisville, and Dr. H. H. Shoulders, Nashville, a course was conducted at the Dyersburg (Tenn.) Army Air Base and the Kennedy General Hospital, Memphis, Tenn., September 20, 21, 22, 23, 24 and 25.

Under the Chairmanship of Dr. Carl Mulky, F.A.C.P., Albuquerque, and with his Committee consisting of Dr. Fred G. Holmes, F.A.C.P., Phoenix, and Dr. L. B. Cohenour, Albuquerque, a course was conducted October 13–15 at Kirtland Field, Albuquerque, and on October 18–20 at the Davis-Monthan Field, Tucson.

North Carolina A. C. P. Regional Meeting

Under the Chairmanship of Dr. Paul F. Whitaker, F.A.C.P., Kinston, College Governor for North Carolina, a state meeting of the College was held at the Bowman Gray School of Medicine at Winston-Salem, October 29. Dr. Wingate M. Johnson,

F.A.C.P., Winston-Salem, was Chairman of the Program Committee. Not only were members of the College invited to attend, but likewise all medical officers of the armed forces in the territory. The program was as follows:

AFTERNOON SESSION—2:00 p.m.

Amphitheater

Bowman Gray School of Medicine

"The Typhus Fever Problem in North Carolina."
T. W. BAKER, M.D., F.A.C.P., and JAMES M. ALEXANDER, M.D., (Associate, A.C.P.), Charlotte, N. C.

"Coronary Occlusion."
WILLIAM B. DEWAR, M.D., F.A.C.P., Raleigh, N. C.

"Changing Phases in the Treatment of Tuberculosis."
PAUL H. RINGER, M.D., F.A.C.P., Asheville, N. C.

"Clinico-Pathological Conference."
ARTHUR GROLLMAN (by invitation) and ROBERT P. MOREHEAD, M.D., (Associate, A.C.P.), Winston-Salem, N. C.

EVENING PROGRAM

Robert E. Lee Hotel

7:00 Dinner (Informal)

Guest Speaker

WILLIAM B. CASTLE, M.D., F.A.C.P., Boston, Mass.

"As They Were: Colored Pictures of Australia and the East in 1938."

Remarks

CHARLES H. COCKE, M.D., F.A.C.P., First Vice President, A.C.P.
PAUL F. WHITAKER, M.D., F.A.C.P., Governor for North Carolina.

OBITUARIES

DR. HARRO WOLTMANN, F.A.C.P.

Dr. Harro Woltmann of Mansfield, Ohio, died December 27, 1942, of tuberculosis. He was born in Chicago, Ill., October 15, 1882, graduated from the University of Michigan Medical School in 1905, and interned at the University of Michigan Hospital. He was a resident at the Lakeside Hospital, Cleveland, 1905–06. During his earlier years, he did postgraduate work in Boston, New York, Philadelphia and Los Angeles. For many years Dr. Woltmann was Chief of Staff of the Mansfield General Hospital and was actively interested in the work of the Richland County Tuberculosis and Health Association, serving as Chairman of the Program Committee and as a member of its Executive Committee.

He had been a Fellow of the American College of Physicians since 1928, having at that time been sponsored by the late Drs. Aldred Scott Warthin, John Phillips and Frank Smithies.

DR. GUY LEARTUS CONNOR, F.A.C.P.

Dr. Guy Leartus Connor of Detroit, Michigan, died at Fort Lauderdale, Florida, April 19, 1943, of cerebral hemorrhage. He was born at Detroit, October 10, 1874, graduated from Williams College (A.B., 1897), and received his medical degree from Johns Hopkins University School of Medicine in 1901.

For many years he was a member of the staffs of the Children's Hospital of Michigan, Harper Hospital and St. Mary's Hospital, all of Detroit. Formerly he was Assistant Clinical Professor of Neurology, Psychiatry and Preventive Medicine at the Detroit College of Medicine, and at one time Medical Director of the Detroit Board of Education.

Dr. Connor had been a member, and in 1928 President, of the Federation of State Medical Boards. From 1917 to 1929, he was a member of the Michigan State Board of Registration in Medicine, and served as its Secretary from 1924 to 1929. He was a former President of the Michigan State Medical Society, and served some time as the Managing Editor of its journal. He also served for several years as a member of the House of Delegates of the American Medical Association.

Dr. Connor was among the early Fellows (1917) of the American College of Physicians, and maintained an active, interested part in its activities the remainder of his life.

COLONEL EDGAR FREMONT HAINES, (MC), U.S.A.

Colonel Edgar Fremont Haines, (MC), U.S.A., a Fellow of the College, died July 22, 1943, and received a military funeral at the Arlington National Cemetery, Arlington, Va.

Colonel Haines was born at Fairhaven, Mass., March 10, 1883. He graduated from the Boston University School of Medicine in 1906 and immediately thereafter entered the Medical Corps of the U. S. Army, and served continuously for thirty-three years. During his tour of duty, Colonel Haines served in the Philippine Islands, in Mexico and in China. His decorations included the Mexican and the Expeditionary medals. In the course of his career he studied at the Army Medical Field Service School at Carlisle Barracks, Carlisle, Pa., and for a time was Professor of Military Medicine at Boston University School of Medicine. He traveled extensively throughout this Country, and his foreign duty came in 1910 with the 13th Infantry in Davao, P. I. He was later transferred to China, where he served during the Revolution in 1913. He was the Attending Surgeon at the Army Base in Boston for six years and the Surgeon of the Army War College in Washington, D. C., for four years. His last assignment was to direct the activation of the Station Hospital at Fort Dix, N. J.

Colonel Haines was a member of the Association of Military Surgeons, the American Medical Association and the Military Order of Carabao. He had been a Fellow of the American College of Physicians since 1932. He is survived by his wife, Nathalie, of Brookline, Mass., by a daughter, Mrs. Donald F. Taylor, wife of a Coast Artillery Captain, and two brothers, Dr. G. A. Haines, of Everett, Mass., and Mr. Herbert Haines, of Lowell, Mass.